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(54) Title: NOVEL COMPOUNDS AND COMPOSITIONS AS CATHEPSIN INHIBITORS

(57) Abstract: The present invention relates to compounds of formula I, where the variables are as defined in Claim 1, process for their preparation and their use as cathepsin S inhibitors.

-1-

NOVEL COMPOUNDS AND COMPOSITIONS AS CATHEPSIN INHIBITORS

THE INVENTION

This application is based on and claims priority from U.S. Provisional Application
5 S.N. 60/322,318 filed on September 14, 2001, incorporated herein by reference.

This Application relates to compounds and compositions for treating diseases
associated with cysteine protease activity, particularly diseases associated with activity of
cathepsin S.

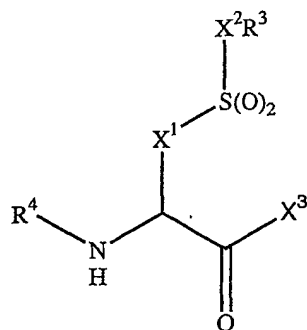
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DESCRIPTION OF THE FIELD

Cysteine proteases represent a class of peptidases characterized by the presence of
a cysteine residue in the catalytic site of the enzyme. Cysteine proteases are associated
15 with the normal degradation and processing of proteins. The aberrant activity of cysteine
proteases, e.g., as a result of increase expression or enhanced activation, however, may
have pathological consequences. In this regard, certain cysteine proteases are associated
with a number of disease states, including arthritis, muscular dystrophy, inflammation,
tumor invasion, glomerulonephritis, malaria, periodontal disease, metachromatic
20 leukodystrophy and others. An increase in cathepsin S activity contributes to the pathology
and/or symptomatology of a number of diseases. Accordingly, molecules that inhibit the
activity of cathepsin S protease are useful as therapeutic agents in the treatment of such
diseases.

SUMMARY OF THE INVENTION

This Application relates to compounds of Formula I:



I

in which:

X^1 and X^2 are both methylene or X^1 is ethylene and X^2 is a bond;

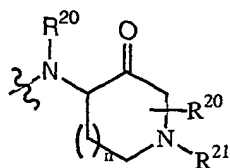
- R^3 is $-CR^5=CHR^6$, $-CR^5(CR^6_3)_2$ or $-CR^7=NR^8$, wherein R^5 is hydrogen and R^6 is hydrogen or (C_{1-4}) alkyl or R^5 and R^6 together with the atoms to which R^5 and R^6 are attached form (C_{3-12}) cycloalkenyl, hetero (C_{5-12}) cycloalkenyl, (C_{6-12}) aryl, hetero (C_{6-12}) aryl, (C_{9-12}) bicycloaryl or hetero (C_{8-12}) bicycloaryl and R^7 and R^8 together with the atoms to which R^7 and R^8 are attached form hetero (C_{5-12}) cycloalkenyl, hetero (C_{6-12}) aryl or hetero (C_{8-12}) bicycloaryl, wherein R^3 optionally is substituted by 1 to 5 radicals independently selected from a group consisting of (C_{1-4}) alkyl, cyano, halo, halo-substituted (C_{1-4}) alkyl, nitro, $-X^4NR^9R^9$, $-X^4OR^9$, $-X^4SR^9$, $-X^4C(O)NR^9R^9$, $-X^4C(O)OR^9$, $-X^4S(O)R^{10}$, $-X^4S(O)_2R^{10}$ and $-X^4C(O)R^{10}$, wherein X^4 is a bond or (C_{1-2}) alkylene, R^9 at each occurrence independently is hydrogen, (C_{1-3}) alkyl or halo-substituted (C_{1-3}) alkyl and R^{10} is (C_{1-3}) alkyl or halo-substituted (C_{1-3}) alkyl; and

R^4 is $-C(O)X^5R^{11}$ or $-S(O)_2X^5R^{11}$, wherein X^5 is a bond, $-O-$ or $-NR^{12}-$, wherein R^{12} is hydrogen or (C_{1-6}) alkyl, and R^{11} is (i) (C_{1-6}) alkyl optionally substituted by $-OR^{13}$, $-SR^{13}$, $-S(O)R^{13}$, $-S(O)_2R^{13}$, $-C(O)R^{13}$, $-C(O)OR^{13}$, $-C(O)NR^{13}R^{14}$, $-NR^{13}R^{14}$, $-NR^{14}C(O)R^{13}$, $-NR^{14}C(O)OR^{13}$, $-NR^{14}C(O)NR^{13}R^{14}$ or $-NR^{14}C(NR^{14})NR^{13}R^{14}$, wherein R^{13} is
5 (C_{3-12}) cycloalkyl (C_{0-3}) alkyl, hetero (C_{5-12}) cycloalkyl (C_{0-3}) alkyl, (C_{6-12}) aryl (C_{0-3}) alkyl, hetero (C_{5-12}) aryl (C_{0-3}) alkyl, (C_{9-12}) bicycloaryl (C_{0-3}) alkyl or hetero (C_{8-12}) bicycloaryl (C_{0-3}) alkyl and R^{14} at each occurrence independently is hydrogen or (C_{1-6}) alkyl, or (ii) (C_{3-12}) cycloalkyl (C_{0-3}) alkyl, hetero (C_{5-12}) cycloalkyl (C_{0-3}) alkyl, (C_{6-12}) aryl (C_{0-3}) alkyl, hetero (C_{5-12}) aryl (C_{0-3}) alkyl, (C_{9-12}) bicycloaryl (C_{0-3}) alkyl or
10 hetero (C_{8-12}) bicycloaryl (C_{0-3}) alkyl or (iii) (C_{3-6}) cycloalkyl (C_{0-3}) alkyl, hetero (C_{5-6}) cycloalkyl (C_{0-3}) alkyl, phenyl (C_{0-3}) alkyl or hetero (C_{5-6}) aryl (C_{0-3}) alkyl substituted by $-X^6OR^{15}$, $-X^6SR^{15}$, $-X^6S(O)R^{15}$, $-X^6S(O)_2R^{15}$, $-X^6C(O)R^{15}$, $-X^6C(O)OR^{15}$, $-X^6C(O)NR^{15}R^{16}$, $-X^6NR^{15}R^{16}$, $-X^6NR^{16}C(O)R^{15}$, $-X^6NR^{16}C(O)OR^{15}$, $-X^6NR^{16}C(O)NR^{15}R^{16}$, $-X^6NR^{16}C(O)OR^{16}$, $-X^6NR^{16}C(NR^{16})NR^{15}R^{16}$, wherein X^6 is a
15 bond or methylene, R^{15} is (C_{3-6}) cycloalkyl (C_{0-3}) alkyl, hetero (C_{5-6}) cycloalkyl (C_{0-3}) alkyl, phenyl (C_{0-3}) alkyl or hetero (C_{5-6}) aryl (C_{0-3}) alkyl and R^{16} is hydrogen or (C_{1-6}) alkyl; wherein R^4 optionally further contains 1 to 5 substituents which when occurring within an alicyclic or aromatic ring system are radicals independently selected from a group consisting of (C_{1-6}) alkyl, (C_{1-6}) alkylidene, cyano, halo, nitro, halo-substituted (C_{1-3}) alkyl, $-X^6NR^{17}R^{17}$,
20 $-X^6NR^{17}C(O)OR^{17}$, $-X^6NR^{17}C(O)NR^{17}R^{17}$, $-X^6NR^{17}C(NR^{17})NR^{17}R^{17}$, $-X^6OR^{17}$, $-X^6SR^{17}$, $-X^6C(O)OR^{17}$, $-X^6C(O)NR^{17}R^{17}$, $-X^6S(O)_2NR^{17}R^{17}$, $-X^6P(O)(OR^{18})OR^{17}$, $-X^6OP(O)(OR^{18})OR^{17}$, $-X^6NR^{17}C(O)R^{18}$, $-X^6S(O)R^{18}$, $-X^6S(O)_2R^{18}$ and $-X^6C(O)R^{18}$ and when occurring within an aliphatic moiety are radicals independently selected from a group consisting of cyano, halo, nitro, $-NR^{17}R^{17}$, $-NR^{17}C(O)OR^{17}$, $-NR^{17}C(O)NR^{17}R^{17}$,

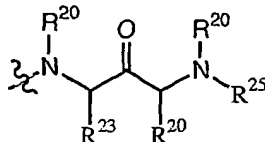
$-\text{NR}^{17}\text{C}(\text{NR}^{17})\text{NR}^{17}\text{R}^{17}$, $-\text{OR}^{17}$, $-\text{SR}^{17}$, $-\text{C}(\text{O})\text{OR}^{17}$, $-\text{C}(\text{O})\text{NR}^{17}\text{R}^{17}$, $-\text{S}(\text{O})_2\text{NR}^{17}\text{R}^{17}$,
 $-\text{P}(\text{O})(\text{OR}^{17})\text{OR}^{17}$, $-\text{OP}(\text{O})(\text{OR}^{17})\text{OR}^{17}$, $-\text{NR}^{17}\text{C}(\text{O})\text{R}^{18}$, $-\text{S}(\text{O})\text{R}^{18}$, $-\text{S}(\text{O})_2\text{R}^{18}$ and $-\text{C}(\text{O})\text{R}^{18}$,
 wherein X^6 is a bond or (C_{1-6}) alkylene, R^{17} at each occurrence independently is hydrogen,
 (C_{1-6}) alkyl or halo-substituted (C_{1-3}) alkyl and R^{18} is (C_{1-6}) alkyl or halo-substituted

5 (C_{1-3}) alkyl;

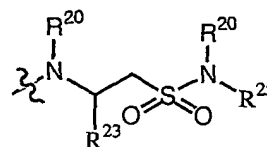
X^3 is a group of Formula (a), (b), (c), (d), (e), (f), (g) or (h):



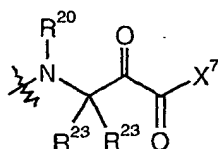
(a)



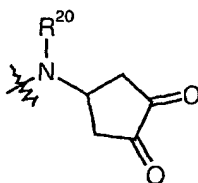
(b)



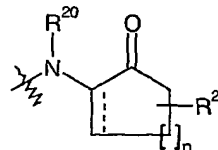
(c)



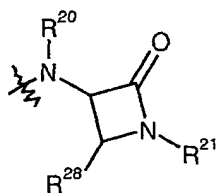
(d)



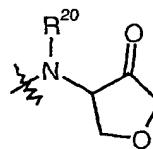
(e)



(f)



(g)



(h)

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--- represents a single bond, or a double bond;

X^7 represents aryl, heteroaryl or $\text{NR}^{20}\text{R}^{25}$;

n is 0, 1 or 2;

R^{20} is selected from the group consisting of hydrogen, (C_{1-6}) alkyl,

(C₃₋₁₂)cycloalkyl(C₀₋₆)alkyl, hetero(C₅₋₁₂)cycloalkyl(C₀₋₆)alkyl, (C₆₋₁₂)aryl(C₀₋₆)alkyl and hetero(C₅₋₁₂)aryl(C₀₋₆)alkyl;

R²¹ is selected from the group consisting of hydrogen, (C₁₋₉)alkyl, (C₃₋₁₂)cycloalkyl(C₀₋₆)alkyl, hetero(C₅₋₁₂)cycloalkyl(C₀₋₆)alkyl, (C₆₋₁₂)aryl(C₀₋₆)alkyl, hetero(C₅₋₁₂)aryl(C₀₋₆)alkyl, (C₉₋₁₂)bicycloaryl(C₀₋₃)alkyl, hetero(C₈₋₁₂)-bicycloaryl(C₀₋₃)alkyl, -C(O)R²⁶, -C(S)R²⁶, -S(O)₂R²⁶, -C(O)OR²⁶, -C(O)N(R²⁶)R²⁷, -C(S)N(R²⁶)R²⁷ and -S(O)₂N(R²⁷)R²⁶;

R²³ is selected from -H, (C₁₋₆)alkyl, (C₄₋₆)alkenyl, (C₃₋₁₂)cycloalkyl(C₀₋₆)alkyl, hetero(C₅₋₁₂)cycloalkyl(C₀₋₆)alkyl, (C₆₋₁₂)aryl(C₀₋₆)alkyl or hetero(C₅₋₁₂)aryl(C₀₋₆)alkyl optionally substituted with amino, -NHC(O)R¹⁵ or -R¹⁵ wherein R¹⁵ is as described above;

R²⁵ is selected from hydrogen, (C₁₋₆)alkyl, (C₃₋₁₂)cycloalkyl(C₀₋₆)alkyl, hetero(C₅₋₁₂)cycloalkyl(C₀₋₆)alkyl, (C₆₋₁₂)aryl(C₀₋₆)alkyl, hetero(C₅₋₁₃)aryl(C₀₋₆)alkyl, -X⁴NHR¹⁵, -X⁴S(O)₂R²⁶ or -X⁴C(O)R¹⁷NR¹⁷C(O)R¹⁷ wherein R¹⁵, R¹⁷ and X⁴ are as described above;

R²⁶ is selected from the group consisting of hydrogen, (C₁₋₆)alkyl, (C₃₋₁₂)cycloalkyl(C₀₋₆)alkyl, hetero(C₅₋₁₂)cycloalkyl(C₀₋₆)alkyl, (C₆₋₁₂)aryl(C₀₋₆)alkyl, hetero(C₅₋₁₂)aryl(C₀₋₆)alkyl, (C₉₋₁₂)bicycloaryl(C₀₋₃)alkyl and hetero(C₈₋₁₂)-bicycloaryl(C₀₋₃)alkyl;

R²⁷ is hydrogen, (C₁₋₆)alkyl, (C₃₋₁₂)cycloalkyl(C₀₋₆)alkyl, hetero(C₅₋₁₂)cycloalkyl(C₀₋₆)alkyl, (C₆₋₁₂)aryl(C₀₋₆)alkyl or hetero(C₅₋₁₂)aryl(C₀₋₆)alkyl;

R²⁸ is R²⁰ or -O-C(=O)-R²⁹;

R²⁹ is (C₁₋₆)alkyl, (C₃₋₁₂)cycloalkyl(C₀₋₃)alkyl, hetero(C₅₋₁₂)cycloalkyl(C₀₋₃)alkyl, (C₆₋₁₂)aryl(C₀₋₃)alkyl, hetero(C₅₋₁₂)aryl(C₀₋₃)alkyl, (C₉₋₁₂)bicycloaryl(C₀₋₃)alkyl or hetero(C₈₋₁₂)bicycloaryl(C₀₋₃)alkyl;

wherein X^3 optionally further contains 1 to 5 substituents which when occurring within an alicyclic or aromatic ring system are radicals independently selected from a group consisting of (C_{1-6}) alkyl, (C_{1-6}) alkylidene, cyano, halo, nitro, halo-substituted (C_{1-3}) alkyl, $-X^6NR^{17}R^{17}$, $-X^6NR^{17}C(O)OR^{17}$, $-X^6NR^{17}C(O)NR^{17}R^{17}$,
 5 $-X^6NR^{17}C(NR^{17})NR^{17}R^{17}$, $-X^6OR^{17}$, $-X^6C(O)R^{17}$, $-X^6OR^{15}$, $-X^6SR^{17}$, $-X^6C(O)OR^{17}$,
 $-X^6C(O)NR^{17}R^{17}$, $-X^6S(O)_2NR^{17}R^{17}$, $-X^6P(O)(OR^8)OR^{17}$, $-X^6OP(O)(OR^8)OR^{17}$,
 $-X^6NR^{17}C(O)R^{18}$, $-X^6S(O)R^{18}$, $-X^6S(O)_2R^{18}$ and $-X^6C(O)R^{18}$ and when occurring within an aliphatic moiety are radicals independently selected from a group consisting of cyano, halo, nitro, $-NR^{17}R^{17}$, $-NR^{17}C(O)OR^{17}$, $-NR^{17}C(O)NR^{17}R^{17}$, $-NR^{17}C(NR^{17})NR^{17}R^{17}$, $-OR^{17}$,
 10 $-SR^{17}$, $-C(O)OR^{17}$, $-C(O)NR^{17}R^{17}$, $-S(O)_2NR^{17}R^{17}$, $-P(O)(OR^{17})OR^{17}$, $-OP(O)(OR^{17})OR^{17}$,
 $-NR^{17}C(O)R^{18}$, $-S(O)R^{18}$, $-S(O)_2R^{18}$ and $-C(O)R^{18}$, wherein R^{15} , R^{17} , R^{18} and X^6 are as described above.

A second aspect of the invention is a pharmaceutical composition that contains a compound of Formula I or their *N*-oxide derivatives, individual isomers or mixture of
 15 isomers thereof, or pharmaceutically acceptable salts thereof, in admixture with one or more suitable excipients.

A third aspect of the invention is a method for treating a disease in an animal in which inhibition of cathepsin S can prevent, inhibit or ameliorate the pathology and/or symptomatology of the disease, which method comprises administering to the animal a
 20 therapeutically effective amount of compound of Formula I or a *N*-oxide derivative, individual isomer or mixture of isomers thereof; or a pharmaceutically acceptable salt thereof.

A fourth aspect of the invention is the processes for preparing compounds of Formula I and the *N*-oxide derivatives, prodrug derivatives, protected derivatives,

individual isomers and mixtures of isomers thereof; and the pharmaceutically acceptable salts thereof.

DETAILED DESCRIPTION OF THE INVENTION

5

Definitions:

Unless otherwise stated, the following terms used in the specification and claims are defined for the purposes of this Application and have the following meanings.

10 "Alicyclic" means a moiety characterized by arrangement of the carbon atoms in closed non-aromatic ring structures having properties resembling those of aliphatics and may be saturated or partially unsaturated with two or more double or triple bonds.

"Aliphatic" means a moiety characterized by a straight or branched chain arrangement of the constituent carbon atoms and may be saturated or partially unsaturated
15 with two or more double or triple bonds.

"Alkyl" represented by itself means a straight or branched, saturated or unsaturated, aliphatic radical having the number of carbon atoms indicated (e.g., (C₁₋₆)alkyl includes methyl, ethyl, propyl, isopropyl, butyl, *sec*-butyl, isobutyl, *tert*-butyl, vinyl, allyl, 1-propenyl, isopropenyl, 1-butenyl, 2-butenyl, 3-butenyl, 2-methylallyl, ethynyl,
20 1-propynyl, 2-propynyl, and the like). Alkyl represented along with another radical (e.g., as in arylalkyl) means a straight or branched, saturated or unsaturated aliphatic divalent radical having the number of atoms indicated or when no atoms are indicated means a bond (e.g., (C₆₋₁₀)aryl(C₀₋₃)alkyl includes phenyl, benzyl, phenethyl, 1-phenylethyl 3-phenylpropyl, and the like).

"Alkylene", unless indicated otherwise, means a straight or branched, saturated or unsaturated, aliphatic, divalent radical having the number of carbon atoms indicated (e.g., (C₁₋₆)alkylene includes methylene (-CH₂-), ethylene (-CH₂CH₂-), trimethylene (-CH₂CH₂CH₂-), tetramethylene (-CH₂CH₂CH₂CH₂-), 2-butenylene (-CH₂CH=CHCH₂-),
5 2-methyltetramethylene (-CH₂CH(CH₃)CH₂CH₂-), pentamethylene (-CH₂CH₂CH₂CH₂CH₂-) and the like).

"Alkylidene" means a straight or branched saturated or unsaturated, aliphatic, divalent radical having the number of carbon atoms indicated (e.g. (C₁₋₆)alkylidene includes methylene (=CH₂), ethylidene (=CHCH₃), isopropylidene (=C(CH₃)₂),
10 propylidene (=CHCH₂CH₃), allylidene (=CH-CH=CH₂), and the like).

"Amino" means the radical -NH₂. Unless indicated otherwise, the compounds of the invention containing amino moieties include protected derivatives thereof. Suitable protecting groups for amino moieties include acetyl, *tert*-butoxycarbonyl, benzyloxycarbonyl, and the like.

15 "Animal" includes humans, non-human mammals (e.g., dogs, cats, rabbits, cattle, horses, sheep, goats, swine, deer, and the like) and non-mammals (e.g., birds, and the like).

"Aromatic" means a moiety wherein the constituent atoms make up an unsaturated ring system, all atoms in the ring system are *sp*² hybridized and the total number of pi electrons is equal to 4n+2.

20 "Aryl" means a monocyclic or fused bicyclic ring assembly containing the total number of ring carbon atoms indicated, wherein each ring is comprised of 6 ring carbon atoms and is aromatic or when fused with a second ring forms an aromatic ring assembly. For example, optionally substituted (C₆₋₁₀)aryl as used in this Application includes, but is not limited to, biphenyl-2-yl, 2-bromophenyl, 2-bromocarbonylphenyl, 2-bromo-

5-fluorophenyl, 4-*tert*-butylphenyl, 4-carbamoylphenyl, 4-carboxy-2-nitrophenyl, 2-chlorophenyl, 4-chlorophenyl, 3-chlorocarbonylphenyl, 4-chlorocarbonylphenyl, 2-chloro-4-fluorophenyl, 2-chloro-6-fluorophenyl, 4-chloro-2-nitrophenyl, 6-chloro-2-nitrophenyl, 2,6-dibromophenyl, 2,3-dichlorophenyl, 2,5-dichlorophenyl, 3,4-dichlorophenyl, 2-difluoromethoxyphenyl, 3,5-dimethylphenyl, 2-ethoxycarbonylphenyl, 2-fluorophenyl, 2-iodophenyl, 4-isopropylphenyl, 2-methoxyphenyl, 4-methoxyphenyl, 2-methylphenyl, 3-methylphenyl, 4-methylphenyl, 5-methyl-2-nitrophenyl, 4-methylsulfonylphenyl, naphth-2-yl, 2-nitrophenyl, 3-nitrophenyl, 4-nitrophenyl, 2,3,4,5,6-pentafluorophenyl, phenyl, 2-trifluoromethoxyphenyl, 3-trifluoromethoxyphenyl, 4-trifluoromethoxyphenyl, 2-trifluoromethylphenyl, 3-trifluoromethylphenyl, 4-trifluoromethylphenyl, 2-trifluoromethylsulfanylphenyl, 4-trifluoromethylsulfanylphenyl, and the like. Optionally substituted (C₆₋₁₀)aryl as used in this Application includes 3-acetylphenyl, 3-*tert*-butoxycarbonylaminomethylphenyl, biphenyl-4-yl, 3-hydroxyphenyl, 4-hydroxyphenyl, 3-methoxyphenyl, naphth-2-yl, 3-phenoxyphenyl, phenyl, and the like.

"Bicycloaryl" means a bicyclic ring assembly containing the number of ring carbon atoms indicated, wherein the rings are linked by a single bond or fused and at least one of the rings comprising the assembly is aromatic, and any carbocyclic ketone, thioketone or iminoketone derivative thereof (e.g., (C₉₋₁₀)bicycloaryl includes cyclohexylphenyl, 1,2-dihydronaphthyl, 2,4-dioxo-1,2,3,4-tetrahydronaphthyl, indanyl, indenyl, 1,2,3,4-tetrahydronaphthyl, and the like).

"Carbamoyl" means the radical -C(O)NH₂. Unless indicated otherwise, the compounds of the invention containing carbamoyl moieties include protected derivatives thereof. Suitable protecting groups for carbamoyl moieties include acetyl,

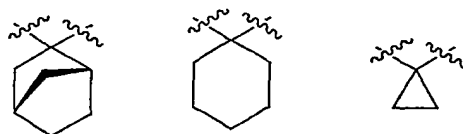
tert-butoxycarbonyl, benzyloxycarbonyl, and the like and both the unprotected and protected derivatives fall within the scope of the invention.

"Carbocyclic ketone derivative" means a derivative containing the moiety -C(O)- .

5 "Carboxy" means the radical -C(O)OH . Unless indicated otherwise, the compounds of the invention containing carboxy moieties include protected derivatives thereof. Suitable protecting groups for carboxy moieties include benzyl, *tert*-butyl, and the like.

"Cycloalkyl" means a saturated or partially unsaturated, monocyclic, fused bicyclic
10 or bridged polycyclic ring assembly containing the number of ring carbon atoms indicated, and any carbocyclic ketone, thioketone or iminoketone derivative thereof (e.g., (C_{3-10}) cycloalkyl includes cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclohexenyl, 2,5-cyclohexadienyl, bicyclo[2.2.2]octyl, adamantan-1-yl, decahydronaphthyl, oxocyclohexyl, dioxocyclohexyl, thiocyclohexyl, 2-oxobicyclo[2.2.1]hept-1-yl, and the
15 like).

"Cycloalkylene" means a divalent saturated or partially unsaturated, monocyclic ring or bridged polycyclic ring assembly containing the number of ring carbon atoms indicated, and any carbocyclic ketone, thioketone or iminoketone derivative thereof. For example, the instance wherein R^1 and R^2 together with the carbon atom to which both R^1
20 and R^2 are attached form (C_{3-8}) cycloalkylene" includes, but is not limited to, the following:



"Disease" specifically includes any unhealthy condition of an animal or part thereof and includes an unhealthy condition that may be caused by, or incident to, medical or veterinary therapy applied to that animal, i.e., the "side effects" of such therapy.

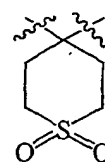
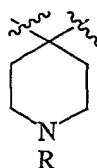
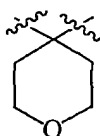
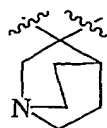
5 "Halo" means fluoro, chloro, bromo or iodo.

"Halo-substituted alkyl", as an isolated group or part of a larger group, means "alkyl" substituted by one or more "halo" atoms, as such terms are defined in this Application. Halo-substituted alkyl includes haloalkyl, dihaloalkyl, trihaloalkyl, perhaloalkyl and the like (e.g. halo-substituted (C₁₋₃)alkyl includes chloromethyl, 10 dichloromethyl, difluoromethyl, trifluoromethyl, 2,2,2-trifluoroethyl, perfluoroethyl, 2,2,2-trifluoro-1,1-dichloroethyl, and the like).

"Heteroatom moiety" includes -N=, -NR-, -N⁺(O⁻)=, -O-, -S- or -S(O)₂-, wherein R is hydrogen, (C₁₋₆)alkyl or a protecting group.

"Heterocycloalkylene" means cycloalkylene, as defined in this Application, 15 provided that one or more of the ring member carbon atoms indicated, is replaced by heteroatom moiety selected from -N=, -NR-, -O-, -S- or -S(O)₂-, wherein R is hydrogen or (C₁₋₆)alkyl. For example, the instance wherein R¹ and R² together with the carbon atom to which both R¹ and R² are attached form hetero(C₃₋₈)cycloalkylene" includes, but is not limited to, the following:

20



in which R is hydrogen, (C₁₋₆)alkyl, or a protecting group.

"Heteroaryl" means aryl, as defined in this Application, provided that one or more of the ring carbon atoms indicated are replaced by a heteroatom moiety selected from -N=, -NR-, -N⁺(O⁻)=, -O- or -S-, wherein R is hydrogen, (C₁₋₆)alkyl, a protecting group or
5 represents the free valence which serves as the point of attachment to a ring nitrogen, and each ring is comprised of 5 or 6 ring atoms. For example, optionally substituted hetero(C₅₋₁₃)aryl as used in this Application includes, but is not limited to, 4-amino-2-hydroxypyrimidin-5-yl, dibenzofuranyl, benzothiazol-2-yl, 1*H*-benzoimidazol-2-yl, 2-bromopyrid-5-yl, 5-bromopyrid-2-yl, 4-carbamoylthiazol-2-yl, 3-carboxypyrid-4-yl,
10 5-carboxy-2,6-dimethylpyrid-3-yl, 3,5-dimethylisoxazol-4-yl, 5-ethoxy-2,6-dimethylpyrid-3-yl, 5-fluoro-6-hydroxypyrimidin-4-yl, fur-2-yl, fur-3-yl, 5-hydroxy-4,6-dimethylpyrid-3-yl, 8-hydroxy-5,7-dimethylquinolin-2-yl, 5-hydroxymethylisoxazol-3-yl, 3-hydroxy-6-methylpyrid-2-yl, 3-hydroxypyrid-2-yl, 1*H*-imidazol-2-yl, 1*H*-imidazol-4-yl, 1*H*-indol-3-yl, isothiazol-4-yl, isoxazol-4-yl,
15 2-methylfur-3-yl, 5-methylfur-2-yl, 1-methyl-1*H*-imidazol-2-yl, 5-methyl-3*H*-imidazol-4-yl, 5-methylisoxazol-3-yl, 5-methyl-2*H*-pyrazol-3-yl, 3-methylpyrid-2-yl, 4-methylpyrid-2-yl, 5-methylpyrid-2-yl, 6-methylpyrid-2-yl, 2-methylpyrid-3-yl, 2-methylthiazol-4-yl, 5-nitropyrid-2-yl, 2*H*-pyrazol-3-yl, 3*H*-pyrazol-4-yl, pyridazin-3-yl, pyrid-2-yl, pyrid-3-yl, pyrid-4-yl, 5-pyrid-3-yl-2*H*-[1,2,4]triazol-3-yl, pyrimidin-4-yl,
20 pyrimidin-5-yl, 1*H*-pyrrol-3-yl, quinolin-2-yl, 1*H*-tetrazol-5-yl, thiazol-2-yl, thiazol-5-yl, thien-2-yl, thien-3-yl, 2*H*-[1,2,4]triazol-3-yl, 3*H*-[1,2,3]triazol-4-yl, 5-trifluoromethylpyrid-2-yl, and the like. Suitable protecting groups include *tert*-butoxycarbonyl, benzyloxycarbonyl, benzyl, 4-methoxybenzyl, 2-nitrobenzyl, and the like. Optionally substituted hetero(C₅₋₁₀)aryl as used in this Application to define R⁴

includes benzofur-2-yl, fur-2-yl, fur-3-yl, pyrid-3-yl, pyrid-4-yl, quinol-2-yl, quinol-3-yl, thien-2-yl, thien-3-yl, and the like.

"Heterobicycloaryl" means bicycloaryl, as defined in this Application, provided that one or more of the ring carbon atoms indicated are replaced by a heteroatom moiety selected from -N=, -NR-, -O- or -S-, wherein R is hydrogen, (C₁₋₆)alkyl, a protecting group or represents the free valence which serves as the point of attachment to a ring nitrogen, and any carbocyclic ketone, thioketone or iminoketone derivative thereof. For example, optionally substituted hetero(C₈₋₁₀)bicycloaryl as used in this Application includes, but is not limited to, 2-amino-4-oxo-3,4-dihydropteridin-6-yl, and the like. In general, the term heterobicycloaryl as used in this Application includes, for example, benzo[1,3]dioxol-5-yl, 3,4-dihydro-2H-[1,8]naphthyridinyl, 3,4-dihydro-2H-quinolinyl, 2,4-dioxo-3,4-dihydro-2H-quinazolinyl, 1,2,3,4,5,6-hexahydro[2,2']bipyridinyl, 3-oxo-2,3-dihydrobenzo[1,4]oxazinyl, 5,6,7,8-tetrahydroquinolinyl, and the like.

"Heterocycloalkyl" means cycloalkyl, as defined in this Application, provided that one or more of the ring carbon atoms indicated are replaced by a heteroatom moiety selected from -N=, -NR-, -O- or -S-, wherein R is hydrogen, (C₁₋₆)alkyl, a protecting group or represents the free valence which serves as the point of attachment to a ring nitrogen, and any carbocyclic ketone, thioketone or iminoketone derivative thereof (e.g., the term hetero(C₅₋₁₀)cycloalkyl includes imidazolidinyl, morpholinyl, piperazinyl, piperidyl, pyrrolidinyl, pyrrolinyl, quinuclidinyl, and the like). Suitable protecting groups include *tert*-butoxycarbonyl, benzyloxycarbonyl, benzyl, 4-methoxybenzyl, 2-nitrobenzyl, and the like. Both the unprotected and protected derivatives fall within the scope of the invention.

"Hydroxy" means the radical -OH. Unless indicated otherwise, the compounds of the invention containing hydroxy radicals include protected derivatives thereof. Suitable

protecting groups for hydroxy moieties include benzyl and the like.

"Iminoketone derivative" means a derivative containing the moiety $-C(NR)-$, wherein R is hydrogen or (C_{1-6}) alkyl.

"Isomers" mean compounds of Formula I having identical molecular formulae but
5 differ in the nature or sequence of bonding of their atoms or in the arrangement of their atoms in space. Isomers that differ in the arrangement of their atoms in space are termed "stereoisomers". Stereoisomers that are not mirror images of one another are termed "diastereomers" and stereoisomers that are nonsuperimposable mirror images are termed "enantiomers" or sometimes "optical isomers". A carbon atom bonded to four nonidentical
10 substituents is termed a "chiral center". A compound with one chiral center has two enantiomeric forms of opposite chirality is termed a "racemic mixture". A compound that has more than one chiral center has 2^{n-1} enantiomeric pairs, where n is the number of chiral centers. Compounds with more than one chiral center may exist as either an individual diastereomers or as a mixture of diastereomers, termed a "diastereomeric mixture". When
15 one chiral center is present a stereoisomer may be characterized by the absolute configuration of that chiral center. Absolute configuration refers to the arrangement in space of the substituents attached to the chiral center. Enantiomers are characterized by the absolute configuration of their chiral centers and described by the *R*- and *S*-sequencing rules of Cahn, Ingold and Prelog. Conventions for stereochemical nomenclature, methods
20 for the determination of stereochemistry and the separation of stereoisomers are well known in the art (e.g., see "Advanced Organic Chemistry", 4th edition, March, Jerry, John Wiley & Sons, New York, 1992). It is understood that the names and illustration used in this Application to describe compounds of Formula I are meant to be encompassed all possible stereoisomers. Thus, for example, the name morpholine-4-carboxylic acid [1-(1-

benzoyl-4-oxo-pyrrolidin-3-ylcarbamoyl)-2-phenylmethanesulfonyl-ethyl]-amide is meant to include morpholine-4-carboxylic acid [S-1-(1-benzoyl-4-oxo-pyrrolidin-3-ylcarbamoyl)-2-phenylmethanesulfonyl-ethyl]-amide and morpholine-4-carboxylic acid [R-1-(1-benzoyl-4-oxo-pyrrolidin-3-ylcarbamoyl)-2-phenylmethanesulfonyl-ethyl]-amide and any mixture, racemic or otherwise, thereof.

"Ketone derivative" means a derivative containing the moiety -C(O)-. For example, for 2-acetoxy-azetidin-3-yl, the "carbocyclic ketone derivative" would be 2-acetoxy-4-oxo-azetidin-3-yl.

"Nitro" means the radical -NO₂.

"Optional" or "optionally" means that the subsequently described event or circumstance may or may not occur, and that the description includes instances where the event or circumstance occurs and instances in which it does not. For example, the phrase "wherein within R³ and R⁴ any alicyclic or aromatic ring system may be substituted further by 1-5 radicals..." means that R³ and R⁴ may or may not be substituted in order to fall within the scope of the invention.

"Oxoalkyl" means alkyl, as defined above, wherein one of the number of carbon atoms indicated is replaced by an oxygen group (-O-), e.g., oxo(C₂₋₆)alkyl includes methoxymethyl, etc.

"N-oxide derivatives" means derivatives of compounds of Formula I in which nitrogens are in an oxidized state (i.e., O-N) and which possess the desired pharmacological activity.

"Pathology" of a disease means the essential nature, causes and development of the disease as well as the structural and functional changes that result from the disease processes.

"Pharmaceutically acceptable" means that which is useful in preparing a pharmaceutical composition that is generally safe, non-toxic and neither biologically nor otherwise undesirable and includes that which is acceptable for veterinary use as well as human pharmaceutical use.

5 "Pharmaceutically acceptable salts" means salts of compounds of Formula I which are pharmaceutically acceptable, as defined above, and which possess the desired pharmacological activity. Such salts include acid addition salts formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like; or with organic acids such as acetic acid, propionic acid, hexanoic acid, 10 heptanoic acid, cyclopentanepropionic acid, glycolic acid, pyruvic acid, lactic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, tartatic acid, citric acid, benzoic acid, *o*-(4-hydroxybenzoyl)benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, 1,2-ethanedisulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, *p*-chlorobenzenesulfonic acid, 2-naphthalenesulfonic acid, 15 *p*-toluenesulfonic acid, camphorsulfonic acid, 4-methylbicyclo[2.2.2]oct-2-ene-1-carboxylic acid, glucoheptonic acid, 4,4'-methylenebis(3-hydroxy-2-ene-1-carboxylic acid), 3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, lauryl sulfuric acid, gluconic acid, glutamic acid, hydroxynaphthoic acid, salicylic acid, stearic acid, muconic acid and the like.

20 Pharmaceutically acceptable salts also include base addition salts which may be formed when acidic protons present are capable of reacting with inorganic or organic bases. Acceptable inorganic bases include sodium hydroxide, sodium carbonate, potassium hydroxide, aluminum hydroxide and calcium hydroxide. Acceptable organic bases include ethanolamine, diethanolamine, triethanolamine, tromethamine, *N*-methylglucamine and the

like.

"Prodrug" means a compound which is convertible in vivo by metabolic means (e.g. by hydrolysis) to a compound of Formula I. For example an ester of a compound of Formula I containing a hydroxy group may be convertible by hydrolysis in vivo to the parent molecule. Alternatively an ester of a compound of Formula I containing a carboxy group may be convertible by hydrolysis in vivo to the parent molecule. Suitable esters of compounds of Formula I containing a hydroxy group, are for example acetates, citrates, lactates, tartrates, malonates, oxalates, salicylates, propionates, succinates, fumarates, maleates, methylene-bis-b-hydroxynaphthoates, gentisates, isethionates, di-*p*-toluoyltartrates, methanesulphonates, ethanesulphonates, benzenesulphonates, *p*-toluenesulphonates, cyclohexylsulphamates and quinate. Suitable esters of compounds of Formula I containing a carboxy group, are for example those described by F.J.Leinweber, Drug Metab. Res., 1987, 18, page 379. An especially useful class of esters of compounds of Formula I containing a hydroxy group, may be formed from acid moieties selected from those described by Bundgaard et al., J. Med. Chem., 1989, 32, page 2503-2507, and include substituted (aminomethyl)-benzoates, for example, dialkylaminomethylbenzoates in which the two alkyl groups may be joined together and/or interrupted by an oxygen atom or by an optionally substituted nitrogen atom, e.g. an alkylated nitrogen atom, more especially (morpholino-methyl)benzoates, e.g. 3- or 4-(morpholinomethyl)-benzoates, and (4-alkylpiperazin-1-yl)benzoates, e.g. 3- or 4-(4-alkylpiperazin-1-yl)benzoates.

"Protected derivatives" means derivatives of compounds of Formula I in which a reactive site or sites are blocked with protecting groups. Protected derivatives of compounds of Formula I are useful in the preparation of compounds of Formula I or in

themselves may be active cathepsin S inhibitors. A comprehensive list of suitable protecting groups can be found in T.W. Greene, *Protecting Groups in Organic Synthesis*, 3rd edition, John Wiley & Sons, Inc. 1999.

"Therapeutically effective amount" means that amount which, when administered
5 to an animal for treating a disease, is sufficient to effect such treatment for the disease.

"Thioketone derivative" means a derivative containing the moiety -C(S)-.

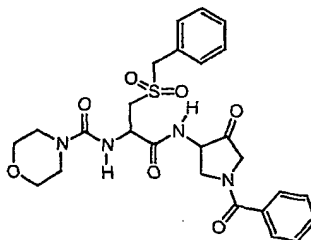
"Treatment" or "treating" means any administration of a compound of the present invention and includes:

- (1) preventing the disease from occurring in an animal which may be predisposed to
10 the disease but does not yet experience or display the pathology or symptomatology of the disease,
- (2) inhibiting the disease in an animal that is experiencing or displaying the pathology or symptomatology of the diseased (i.e., arresting further development of the pathology and/or symptomatology), or
- 15 (3) ameliorating the disease in an animal that is experiencing or displaying the pathology or symptomatology of the diseased (i.e., reversing the pathology and/or symptomatology).

Nomenclature:

20 The compounds of Formula I and the intermediates and starting materials used in their preparation are named in accordance with IUPAC rules of nomenclature in which the characteristic groups have decreasing priority for citation as the principle group as follows: acids, esters, amides, etc. Alternatively, the compounds are named by AutoNom 4.0 (Beilstein Information Systems, Inc.). For example, a compound of Formula I in which R³

is phenyl, R^4 is morpholine-4-carbonyl and X^3 is 1-benzoyl-4-oxo-pyrrolidin-3-ylamino; that is, a compound having the following structure:



- 5 is named morpholine-4-carboxylic acid [1-(1-benzoyl-4-oxo-pyrrolidin-3-ylcarbamoyl)-2-phenylmethanesulfonyl-ethyl]-amide.

Presently Preferred Embodiments:

- While the broadest definition of the invention is set forth in the Summary of the
- 10 Invention, certain aspects of the invention are preferred. For example, for a compound of Formula I, in which X^1 and X^2 are both methylene or X^1 is ethylene and X^2 is a bond; R^3 is $-CR^5=CHR^6$, $-CR^5(CR^6)_2$ or $-CR^7=NR^8$, wherein R^5 is hydrogen and R^6 is hydrogen or (C_{1-4}) alkyl or R^5 and R^6 together with the atoms to which R^5 and R^6 are attached form (C_{3-12}) cycloalkenyl, (C_{6-12}) aryl, hetero (C_{6-12}) aryl or (C_{9-12}) bicycloaryl and R^7 and R^8
- 15 together with the atoms to which R^7 and R^8 are attached form hetero (C_{5-12}) cycloalkenyl or hetero (C_{6-12}) aryl, wherein R^3 optionally is substituted by 1 to 5 radicals independently selected from a group consisting of (C_{1-4}) alkyl, cyano, halo, halo-substituted (C_{1-4}) alkyl, $-X^4OR^9$ and $-X^4C(O)OR^9$, wherein X^4 is a bond or (C_{1-2}) alkylene, R^9 at each occurrence independently is (C_{1-3}) alkyl or halo-substituted (C_{1-3}) alkyl; R^4 is $-C(O)X^5R^{11}$ or
- 20 $-S(O)_2X^5R^{11}$, wherein X^5 is a bond, $-O-$ or $-NR^{12}-$, wherein R^{12} is hydrogen or (C_{1-6}) alkyl, and R^{11} is (i) (C_{1-6}) alkyl or (ii) hetero (C_{5-12}) cycloalkyl (C_{0-3}) alkyl,

(C₆₋₁₂)aryl(C₀₋₃)alkyl, hetero(C₅₋₁₂)aryl(C₀₋₃)alkyl, (C₉₋₁₂)bicycloaryl(C₀₋₃)alkyl or hetero(C₈₋₁₂)bicycloaryl(C₀₋₃)alkyl or (iii) hetero(C₅₋₆)cycloalkyl(C₀₋₃)alkyl or phenyl(C₀₋₃)alkyl substituted by -X⁶OR¹⁵, -X⁶C(O)R¹⁵ or -X⁶NR¹⁶C(O)OR¹⁶, wherein X⁶ is a bond or methylene, R¹⁵ is phenyl(C₀₋₃)alkyl or hetero(C₅₋₆)aryl(C₀₋₃)alkyl and R¹⁶ is hydrogen or (C₁₋₆)alkyl; wherein R⁴ optionally further contains 1 to 5 substituents which when occurring within an alicyclic or aromatic ring system are radicals independently selected from a group consisting of (C₁₋₆)alkyl, halo, -X⁶NR¹⁷R¹⁷, -X⁶OR¹⁷, -X⁶C(O)OR¹⁷, -X⁶NC(O)R¹⁶ and -X⁶C(O)R¹⁸, R¹⁷ at each occurrence independently is hydrogen, (C₁₋₆)alkyl or halo-substituted (C₁₋₃)alkyl and R¹⁸ is (C₁₋₆)alkyl or halo-substituted (C₁₋₃)alkyl.

In particular, X³ is a group of Formula (a), (b) or (c) in which: n is 0, 1 or 2; R²⁰ is selected from the group consisting of hydrogen and (C₁₋₆)alkyl; R²¹ is selected from the group consisting of (C₁₋₉)alkyl, (C₆₋₁₂)aryl(C₀₋₆)alkyl, -C(O)R²⁶, -S(O)₂R²⁶, -C(O)OR²⁶ and -C(O)N(R²⁶)R²⁷; R²³ is selected from (C₁₋₆)alkyl optionally substituted with amino, -NHC(O)R¹⁵ or -R¹⁵ wherein R¹⁵ is as described above; R²⁵ is selected from (C₁₋₆)alkyl, (C₆₋₁₂)aryl(C₀₋₆)alkyl, -X⁴S(O)₂R²⁶ or -X⁴C(O)R¹⁷NR¹⁷C(O)R¹⁷ wherein R¹⁷ and X⁴ are as described above and R²⁶ is as described below; R²⁶ is selected from the group consisting of (C₁₋₆)alkyl, hetero(C₅₋₁₂)cycloalkyl(C₀₋₆)alkyl, (C₆₋₁₂)aryl(C₀₋₆)alkyl, hetero(C₅₋₁₂)aryl(C₀₋₆)alkyl and (C₉₋₁₂)bicycloaryl(C₀₋₃)alkyl; R²⁷ is (C₁₋₆)alkyl; herein X³ optionally further contains 1 to 5 substituents which when occurring within an alicyclic or aromatic ring system are radicals independently selected from a group consisting of (C₁₋₆)alkyl, cyano, halo, -X⁶OR¹⁷, -X⁶C(O)R¹⁷ and -X⁶OR¹⁵.

R³ more preferably is selected from the group consisting of phenyl, pyridin-2-yl, pyridin-3-yl, pyridin-4-yl, vinyl, 2-difluoromethoxyphenyl, 1-oxy-pyridin-2-yl, 4-

methoxyphenyl, 4-methylphenyl, 2-methylphenyl, 4-chlorophenyl, 3,5-dimethylphenyl, 4-trifluoromethylphenyl, 4-trifluoromethoxyphenyl, 2-bromophenyl, naphthalen-2-yl, 3,4-dichlorophenyl, 3-methylphenyl, 3-trifluoromethylphenyl, 3-trifluoromethoxyphenyl, 2,3,4,5,6-pentafluoro-phenyl, 2-fluorophenyl, 2-chlorophenyl, 2-cyano-phenyl, 2-trifluoromethylphenyl, 4-*tert*-butyl-phenyl, 3-chlorophenyl, 4-bromophenyl, 2-fluoro-3-chloro-phenyl, 2-fluoro-3-methyl-phenyl, 3-fluorophenyl, 2,5-difluorophenyl, 3-bromophenyl, 2,5-dichlorophenyl, 2,6-difluorophenyl, 3-cyano-phenyl, 4-cyano-phenyl, 2-trifluoromethoxyphenyl, 2,3-difluorophenyl, biphenyl, 2-bromo-5-fluoro-phenyl, 4-fluorophenyl, 3,4-difluorophenyl, 2,4-difluorophenyl, 2,4,6-trifluorophenyl, 2,4,5-trifluorophenyl, 2,3,4-trifluorophenyl, 2-chloro-5-trifluoromethylphenyl, 2,4-bis-trifluoromethylphenyl, 2,5,6-trifluorophenyl, 2-fluoro-3-trifluoromethylphenyl, 2-fluoro-4-trifluoromethylphenyl, 2-fluoro-5-trifluoromethylphenyl, 2,3,5-trifluorophenyl, 2-fluoro-5-trifluoromethylphenyl, 5-fluoro-2-trifluoromethylphenyl, 4-fluoro-3-trifluoromethylphenyl, 2-methoxyphenyl, 3,5-bis-trifluoromethylphenyl, 4-difluoromethoxyphenyl, 3-difluoromethoxyphenyl, 2,6-dichlorophenyl, 4-carboxyphenyl, cyclohexyl, cyclopropyl, isopropyl, thiophen-2-yl, 5-chloro-thiophen-2-yl and 3,5-dimethyl-isoxazol-4-yl.

R⁴ more preferably is selected from the group consisting of benzoyl, morpholine-4-carbonyl, acetyl, furan-3-carbonyl, 2-methoxy-benzoyl, 3-methoxy-benzoyl, naphthalene-2-carbonyl, benzo[1,3]dioxole-5-carbonyl, 3-pyridin-3-yl-acryloyl, benzofuran-2-carbonyl, furan-2-carbonyl, *tert*-butoxy-carbonyl, biphenyl-4-carbonyl, quinoline-2-carbonyl, quinoline-3-carbonyl, 3-acetyl-benzoyl, 4-phenoxy-benzoyl, 3-hydroxy-benzoyl, 4-hydroxy-benzoyl, pyridine-3-carbonyl, 3-(*tert*-butoxycarbonylamino-methyl)-benzoyl, 4-carbonyl-piperazine-1-carboxylic acid *tert*-butyl ester, 4-carbonyl-piperazine-1-carboxylic acid ethyl ester, 4-(furan-2-carbonyl)-piperazine-1-carbonyl, pyridine-4-carbonyl, 1-oxy-

pyridine-4-carbonyl, 1-oxy-pyridine-3-carbonyl, thiophene-2-carbonyl, thiophene-3-carbonyl, 4-benzoyl-benzoyl, 5-methyl-thiophene-2-carbonyl, 3-chloro-thiophene-2-carbonyl, 3-bromo-thiophene-2-carbonyl, 4-chloro-benzoyl, 3-flouro-4-methoxy-benzoyl, 4-methoxy-benzoyl, 4-triflouromethoxy-benzoyl, 3,4-diflouro-benzoyl, 4-flouro-benzoyl, 3,4-dimethoxy-benzoyl, 3-methyl-benzoyl, 4-bromo-benzoyl, 4-triflouromethyl-benzoyl, 3-benzoyl-benzoyl, cyclopentane-carbonyl, benzo[b]thiophene-2-carbonyl, 3-chloro-benzo[b]thiophene-2-carbonyl, benzenesulfonyl, naphthalene-2-sulfonyl, 5-methyl-thiophene-2-sulfonyl, thiophene-2-sulfonyl, formamyl-methyl ester, 4-methyl-pentanoyl, formamyl-isobutyl ester, formamyl-monoallyl ester, formamyl-isopropyl ester, *N,N*-dimethyl-formamyl, *N*-isopropyl-formamyl, *N*-pyridin-4-yl-formamyl, *N*-pyridin-3-yl-formamyl, 3-phenyl-acryloyl, 1H-indole-5-carbonyl, pyridine-2-carbonyl, pyrazine-2-carbonyl, 3-hydroxy-pyridine-2-carbonyl, 2-amino-pyridine-3-carbonyl, 2-hydroxy-pyridine-3-carbonyl, 6-amino-pyridine-3-carbonyl, 6-hydroxy-pyridine-3-carbonyl, pyridazine-4-carbonyl, 3-phenoxy-benzoyl and 1-oxo-1,3-dihydro-isoindole-2-carbonyl.

15 X^3 more preferably is selected from a group consisting of 4-amino-3-oxo-azepane-1-carboxylic acid benzyl ester, 4-amino-3-oxo-azepane-1-carboxylic acid isobutyl ester, 4-amino-1-benzoyl-azepan-3-one, 4-amino-1-benzenesulfonyl-azepan-3-one, 4-amino-1-(pyridine-2-sulfonyl)-azepan-3-one, 4-amino-1-(1-oxy-pyridine-2-sulfonyl)-azepan-3-one, 4-amino-1-(3,4-dichloro-benzenesulfonyl)-azepan-3-one, 4-amino-1-(2-flouro-benzenesulfonyl)-azepan-3-one, 4-amino-1-(3,4-dimethoxy-benzenesulfonyl)-azepan-3-one, 4-amino-1-(2-cyano-benzenesulfonyl)-azepan-3-one, 4-amino-1-(naphthalene-1-sulfonyl)-azepan-3-one, 4-amino-1-(thiophene-2-sulfonyl)-azepan-3-one, 4-amino-1-(thiazole-2-sulfonyl)-azepan-3-one, 4-amino-1-(pyrrolidine-1-sulfonyl)-azepan-3-one, 4-amino-1-methanesulfonyl-azepan-3-one, 4-amino-1-(pyrrolidine-1-carbonyl)-azepan-3-

20

one, 4-amino-3-oxo-azepane-1-carboxylic-acid-dimethylamide, 4-amino-3-oxo-azepane-1-carboxylic-acid-benzylamide, 4-amino-1-benzyl-azepan-3-one, 4-amino-1-benzyl-piperidin-3-one, 4-amino-1-benzoyl-piperidin-3-one, 4-amino-1-benzoyl-pyrrolidin-3-one, 4-amino-1-benzyl-pyrrolidin-3-one, 4-amino-1-benzenesulfonyl-pyrrolidin-3-one, 4-amino-1-(5-methyl-hexyl)-pyrrolidin-3-one, 1-ethyl-2-oxo-3-(toluene-4-sulfonylamino)-butylamino, 1-ethyl-2-oxo-3-(4-phenoxy-benzenesulfonylamino)-propylamino, 1-ethyl-2-oxo-3-[4-(pyridin-3-yloxy)-benzenesulfonylamino]-propylamino, 3-(dibenzofuran-2-sulfonylamino)-1-ethyl-2-oxo-butylamino, 1-ethyl-3-[4-methyl-2-(4-methyl-pentanoylamino)-pentanoylamino]-2-oxo-propylamino, 5-amino-1-[(4-methoxy-phenylsulfamoyl)-methyl]-pentylamino, 5-benzyloxycarbonylamino-1-[(4-methoxy-phenylsulfamoyl)-methyl]-pentylamino, 1-[(4-methoxy-phenylsulfamoyl)-methyl]-3-phenyl-propylamino, 1-[[4-(1-hydroxy-ethyl)-phenylsulfamoyl]-methyl]-3-phenyl-propylamino, 1-[(4-acetyl-phenylsulfamoyl)-methyl]-3-phenyl-propylamino, 1-[(4-hydroxy-phenylsulfamoyl)-methyl]-3-phenyl-propylamino and 3-phenyl-1-[(2-phenylamino-ethylsulfamoyl)-methyl]-propylamino; and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof; and the pharmaceutically acceptable salts and solvates of such compounds and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof.

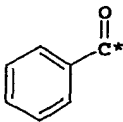
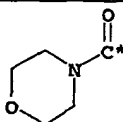

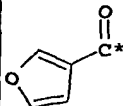
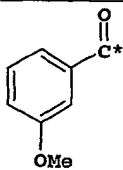
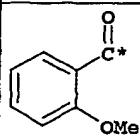
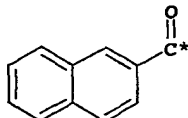
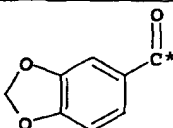
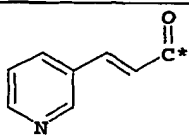
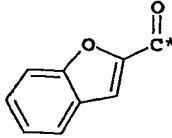
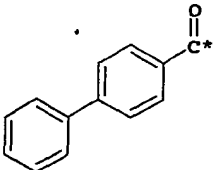
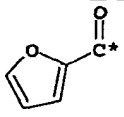
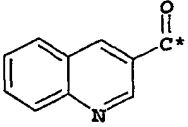
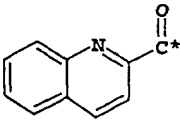

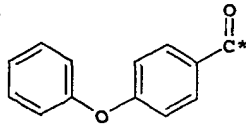
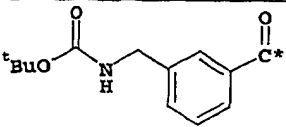
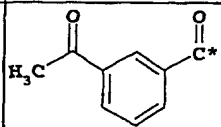
Reference to the preferred embodiments set forth above is meant to include all combinations of particular and preferred groups.

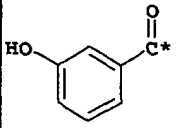
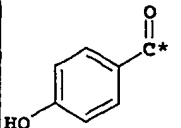
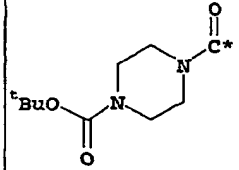
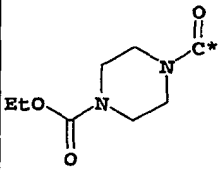
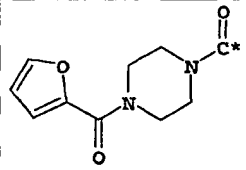
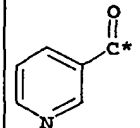
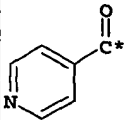
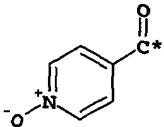
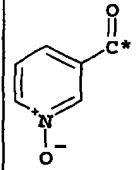
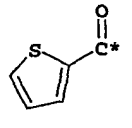
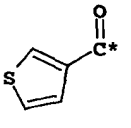
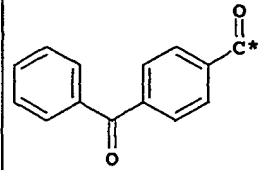
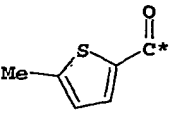
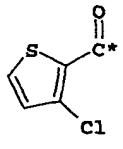
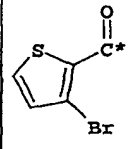
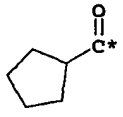
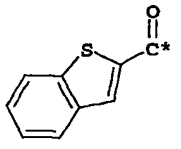
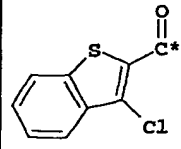
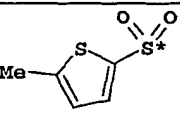
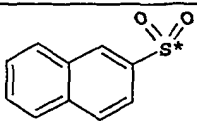
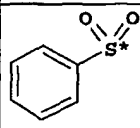
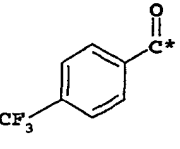
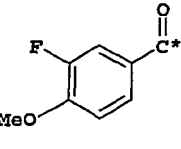
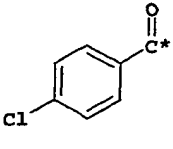
Particular compounds of the invention may be prepared by joining C* of one of the fragments (A1 to A72) shown in Table 1 to the nitrogen atom (*N) of one of the

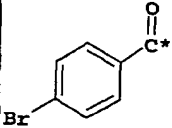
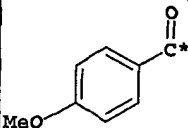
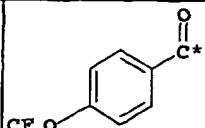
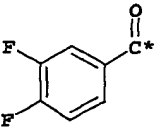
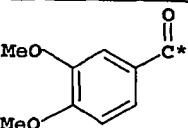
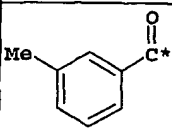
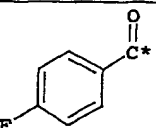
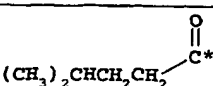
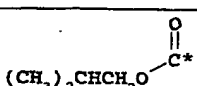

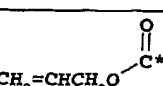
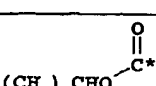
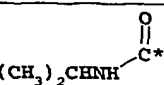
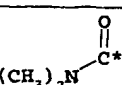
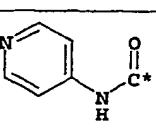
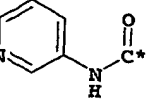
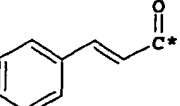
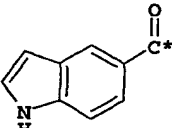
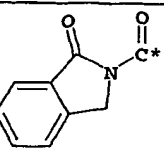
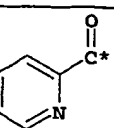
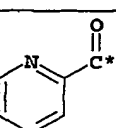
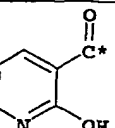
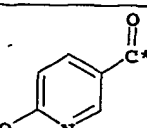
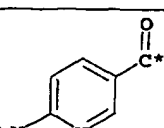
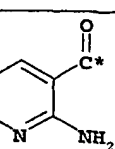
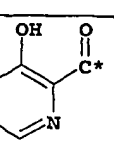
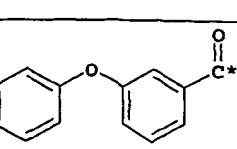
fragments (B1 to B80) shown in Table 2, and joining the methine carbon atom (CH*) of one of the fragments (B1 to B80) shown in Table 2 to the acyl carbon atom (C*) of one of the fragments (C1 to C37) depicted in Table 3.

5

TABLE 1

A1		A2		A3	
A4		A5		A6	
A7		A8		A9	
A10		A11		A12	
A13		A14		A15	
A16		A17		A18	

A19		A20		A21	
A22		A23		A24	
A25		A26		A27	
A28		A29		A30	
A31		A32		A33	
A34		A35		A36	
A37		A38		A39	
A40		A41		A42	

A43		A44		A45	
A46		A47		A48	
A49		A50		A51	
A52		A53		A54	
A55		A56		A57	
A58		A59		A60	
A61		A62		A63	
A64		A65		A66	
A67		A68		A69	

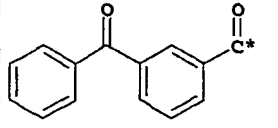
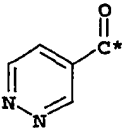
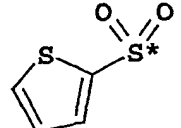
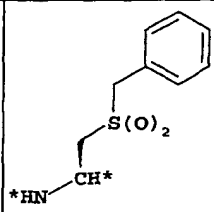
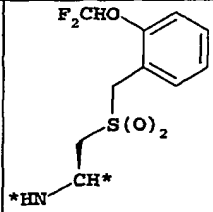
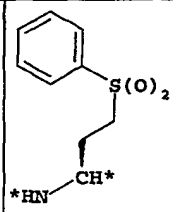
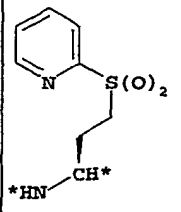
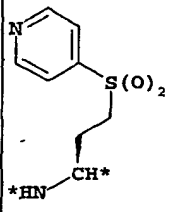
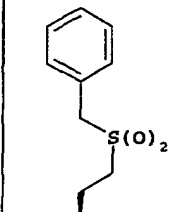
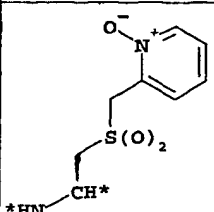
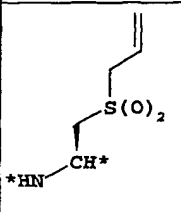
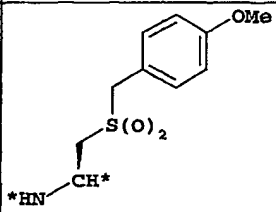
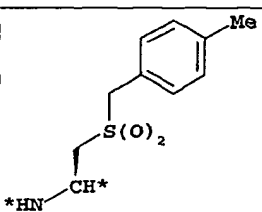
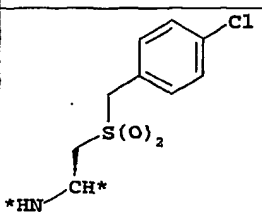
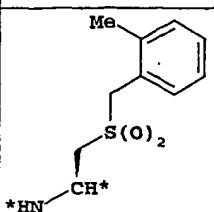
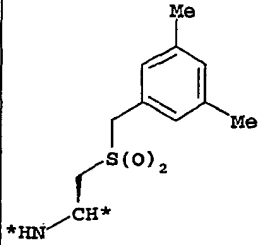
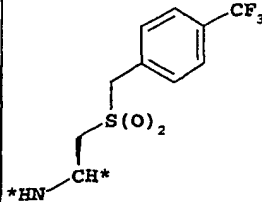
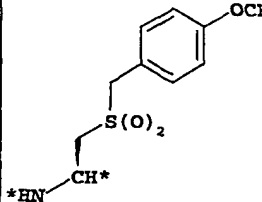
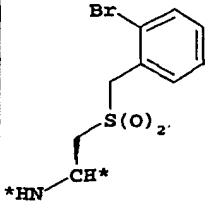
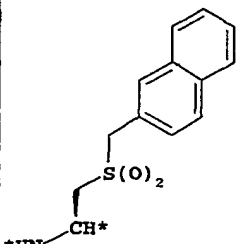
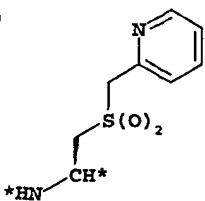
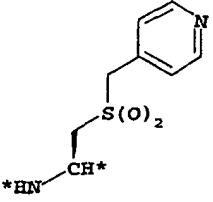
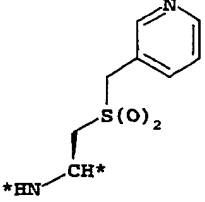
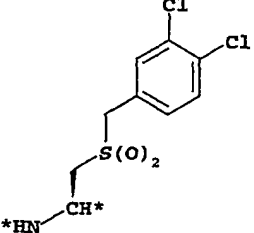
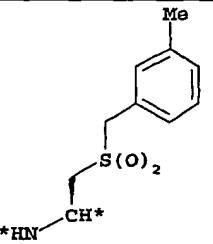
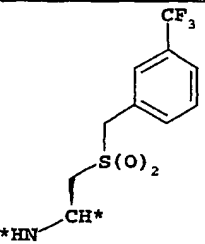
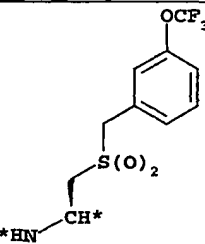
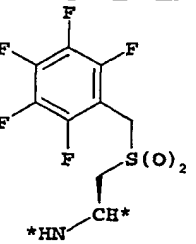
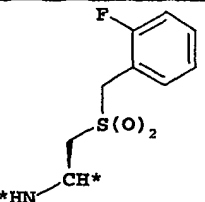
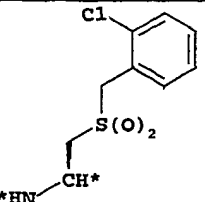
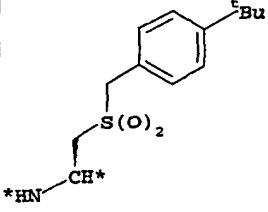
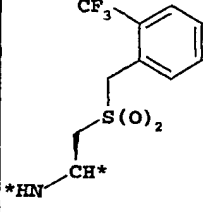
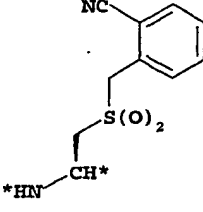
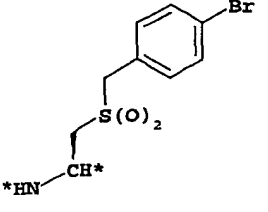
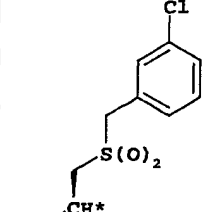
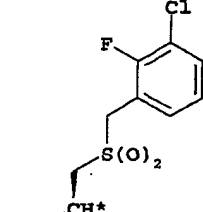
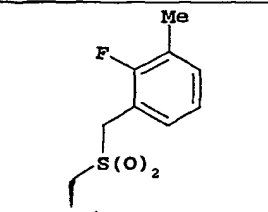
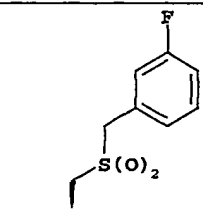
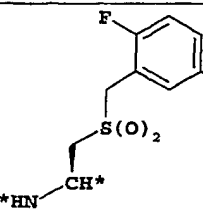
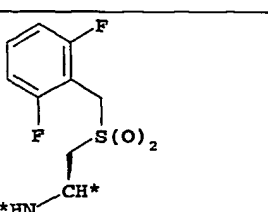
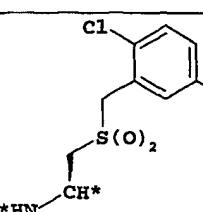
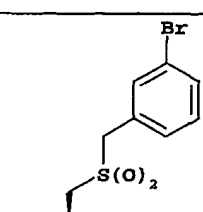
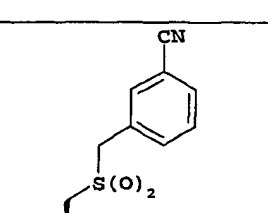
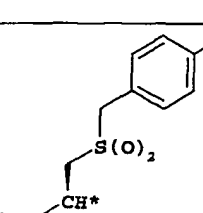
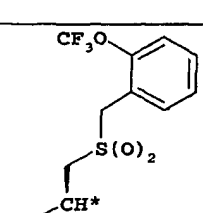
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TABLE 2

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B10		B11		B12	

B13		B14		B15	
B16		B17		B18	
B19		B20		B21	
B22		B23		B24	
B25		B26		B27	

B28		B29		B30	
B31		B32		B33	
B34		B35		B36	
B37		B38		B39	
B40		B41		B42	

B43		B44		B45	
B46		B47		B48	
B49		B50		B51	
B52		B53		B54	
B55		B56		B57	

B58		B59		B60	
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B64		B65		B66	
B67		B68		B69	
B70		B71		B72	

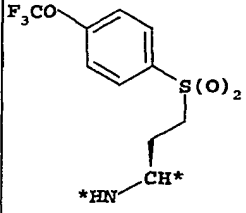
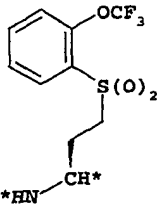
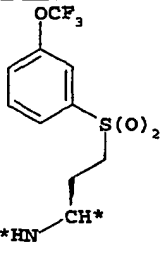
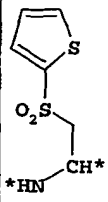
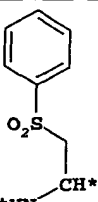
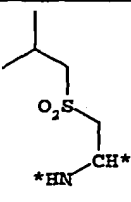
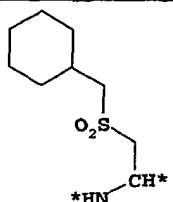
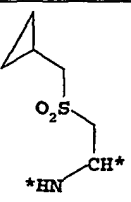
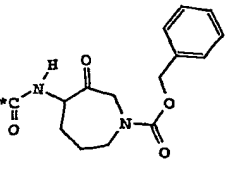
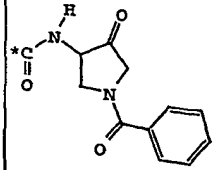
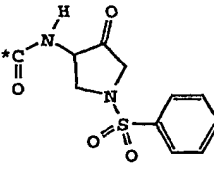
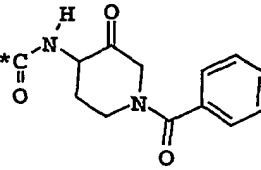
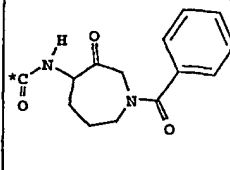
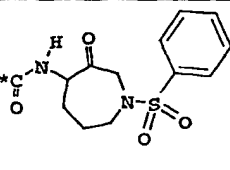
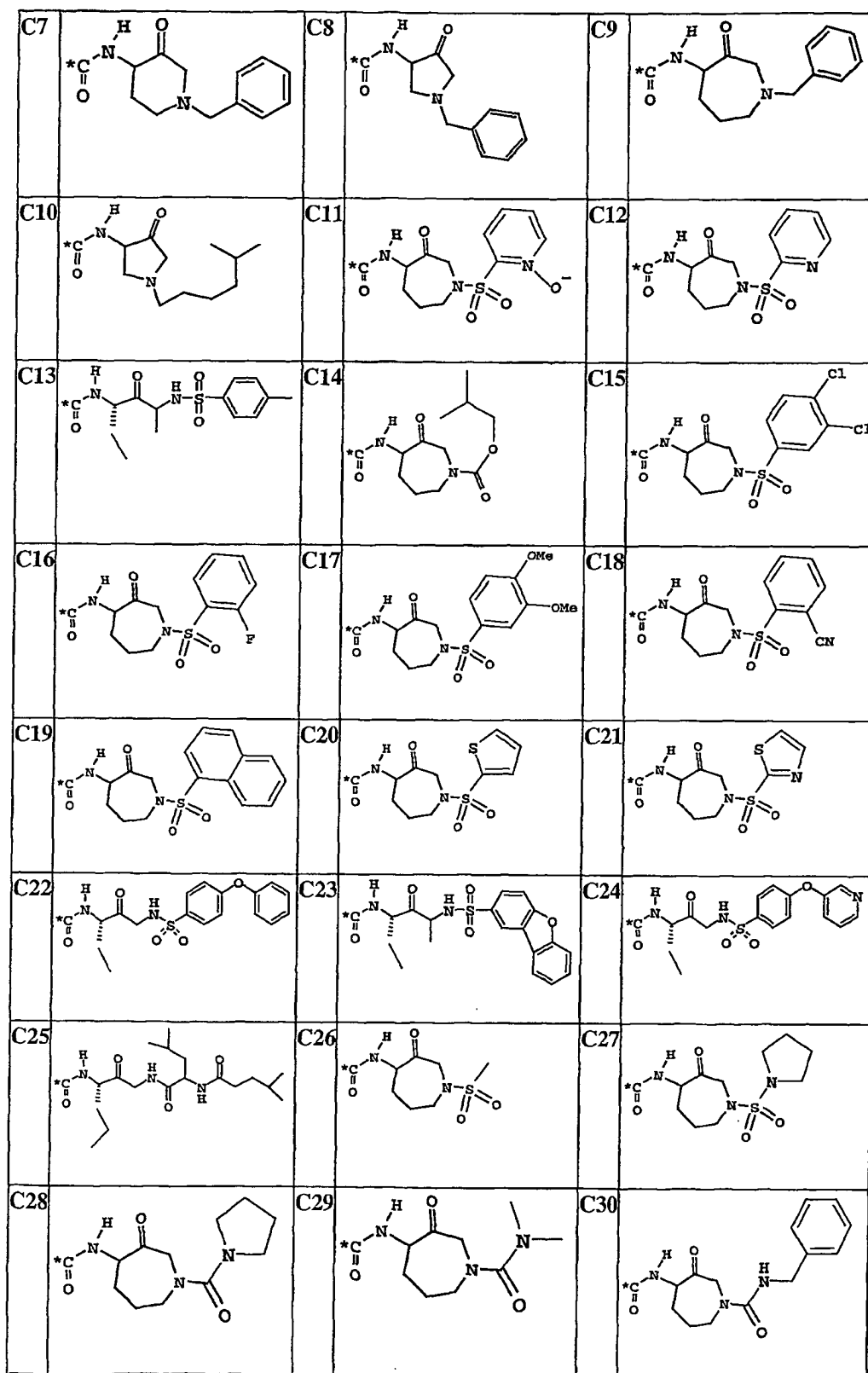
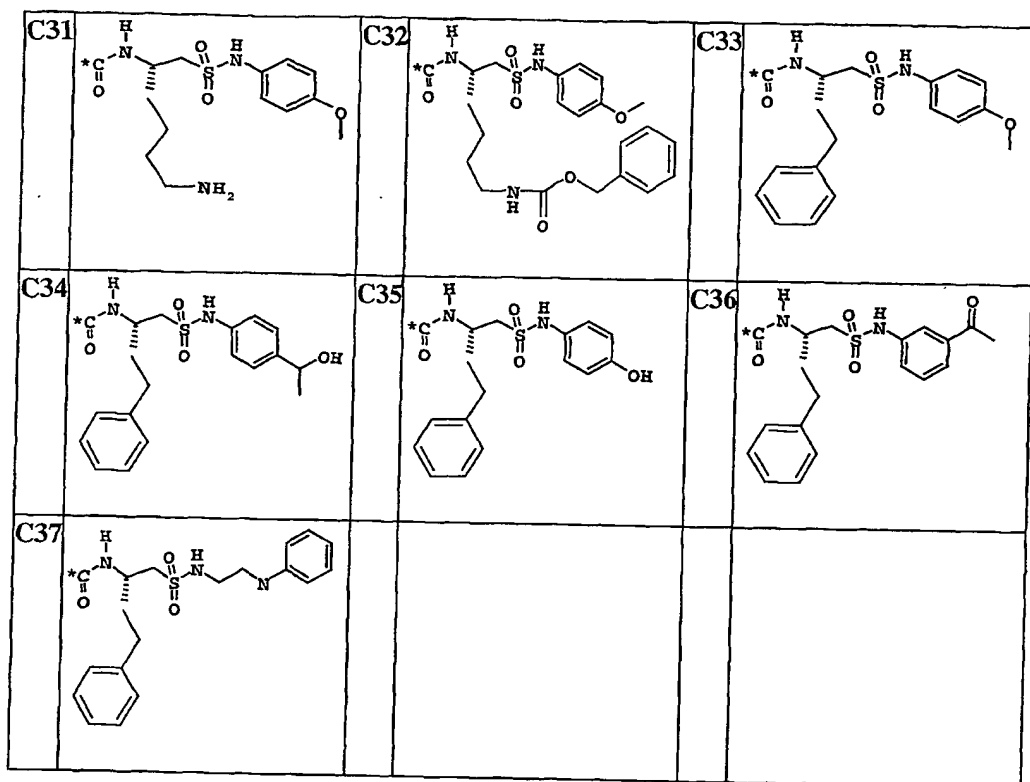
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B76		B77		B78	
B79		B80			

TABLE 3

5

C1		C2		C3	
C4		C5		C6	





Pharmacology and Utility:

The compounds of the invention are selective inhibitors of cathepsin S and, as

5 such, are useful for treating diseases in which cathepsin S activity contributes to the pathology and/or symptomatology of the disease. For example, the compounds of the invention are useful in treating autoimmune disorders, including, but not limited to, juvenile onset diabetes, multiple sclerosis, pemphigus vulgaris, Graves' disease, myasthenia gravis, systemic lupus erythematosus, rheumatoid arthritis and Hashimoto's

10 thyroiditis, allergic disorders, including, but not limited to, asthma, and allogeneic immune responses, including, but not limited to, organ transplants or tissue grafts.

Cathepsin S also is implicated in disorders involving excessive elastolysis, such as chronic obstructive pulmonary disease (e.g., emphysema), bronchiolitis, excessive airway

elastolysis in asthma and bronchitis, pneumonitis and cardiovascular disease such as plaque rupture and atheroma. Cathepsin S is implicated in fibril formation and, therefore, inhibitors of cathepsins S are of use in treatment of systemic amyloidosis.

The cysteine protease inhibitory activities of the compounds of the invention can
5 be determined by methods known to those of ordinary skill in the art. Suitable *in vitro*
assays for measuring protease activity and the inhibition thereof by test compounds are
known. Typically, the assay measures protease induced hydrolysis of a peptide based
substrate. Details of assays for measuring protease inhibitory activity are set forth in
Examples 14-17, *infra*.

10

Administration and Pharmaceutical Compositions:

In general, compounds of Formula I will be administered in therapeutically
effective amounts via any of the usual and acceptable modes known in the art, either singly
or in combination with one or more therapeutic agents. A therapeutically effective amount
15 may vary widely depending on the severity of the disease, the age and relative health of the
subject, the potency of the compound used and other factors. For example, therapeutically
effective amounts of a compound of Formula I may range from about 1 micrograms per
kilogram body weight ($\mu\text{g/kg}$) per day to about 1 milligram per kilogram body weight
(mg/kg) per day, typically from about 10 $\mu\text{g/kg/day}$ to about 0.1 mg/kg/day . Therefore, a
20 therapeutically effective amount for a 80 kg human patient may range from about 100
 $\mu\text{g/day}$ to about 100 mg/day , typically from about 1 $\mu\text{g/day}$ to about 10 mg/day . In general,
one of ordinary skill in the art, acting in reliance upon personal knowledge and the
disclosure of this Application, will be able to ascertain a therapeutically effective amount

of a compound of Formula I for treating a given disease.

The compounds of Formula I can be administered as pharmaceutical compositions by one of the following routes: oral, systemic (e.g., transdermal, intranasal or by suppository) or parenteral (e.g., intramuscular, intravenous or subcutaneous).

5 Compositions can take the form of tablets, pills, capsules, semisolids, powders, sustained release formulations, solutions, suspensions, elixirs, aerosols, or any other appropriate composition and are comprised of, in general, a compound of Formula I in combination with at least one pharmaceutically acceptable excipient. Acceptable excipients are non-toxic, aid administration, and do not adversely affect the therapeutic benefit of the
10 active ingredient. Such excipient may be any solid, liquid, semisolid or, in the case of an aerosol composition, gaseous excipient that is generally available to one of skill in the art.

Solid pharmaceutical excipients include starch, cellulose, talc, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, magnesium stearate, sodium stearate, glycerol monostearate, sodium chloride, dried skim milk, and the like. Liquid and
15 semisolid excipients may be selected from water, ethanol, glycerol, propylene glycol and various oils, including those of petroleum, animal, vegetable or synthetic origin (e.g., peanut oil, soybean oil, mineral oil, sesame oil, and the like). Preferred liquid carriers, particularly for injectable solutions, include water, saline, aqueous dextrose and glycols.

The amount of a compound of Formula I in the composition may vary widely
20 depending upon the type of formulation, size of a unit dosage, kind of excipients and other factors known to those of skill in the art of pharmaceutical sciences. In general, a composition of a compound of Formula I for treating a given disease will comprise from 0.01%w to 10%w, preferably 0.3%w to 1%w, of active ingredient with the remainder being the excipient or excipients. Preferably the pharmaceutical composition is administered in

a single unit dosage form for continuous treatment or in a single unit dosage form ad libitum when relief of symptoms is specifically required. Representative pharmaceutical formulations containing a compound of Formula I are described in Example 10, *infra*.

5

Chemistry:

Processes for Making Compounds of Formula I:

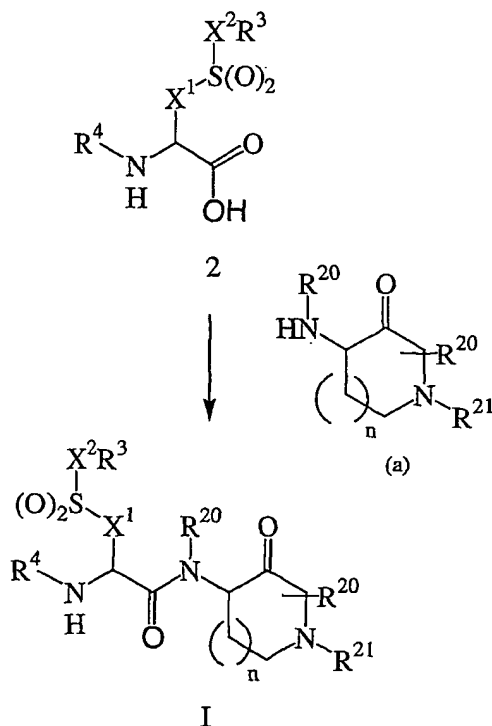
Compounds of the invention may be prepared by the application or adaptation of known methods, by which is meant methods used heretofore or described in the literature, for example those described by R.C. Larock in Comprehensive Organic Transformations, VCH publishers, 1989.

In the reactions described hereinafter it may be necessary to protect reactive functional groups, for example hydroxy, amino, imino, thio or carboxy groups, where these are desired in the final product, to avoid their unwanted participation in the reactions. Conventional protecting groups may be used in accordance with standard practice, for examples see T.W. Greene and P. G. M. Wuts in "Protective Groups in Organic Chemistry" John Wiley and Sons, 1991.

Compounds of Formula I, in which X^3 is a compound of formula (a) (as defined in the Summary of the Invention), can be prepared by proceeding as in the following Reaction Scheme 1:

Reaction Scheme 1

-38-



in which each X^1 , X^2 , R^3 , R^4 , R^{20} and R^{21} are as defined for Formula I in the Summary of the Invention.

- 5 Compounds of Formula I can be prepared by condensing an acid of Formula 2 with an amino compound of formula (a). The condensation reaction can be effected with an appropriate coupling agent (e.g., benzotriazol-1-yloxytrispyrrolidinophosphonium hexafluorophosphate (PyBOP[®]), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI), *O*-benzotriazol-1-yl-*N,N,N',N'*-tetramethyluronium
- 10 hexafluorophosphate (HBTU), 1,3-dicyclohexylcarbodiimide (DCC), or the like) and optionally an appropriate catalyst (e.g., 1-hydroxybenzotriazole (HOBt), 1-hydroxy-7-azabenzotriazole (HOAt), *O*-(7-azabenzotriazol-1-yl)-1,1,3,3, tetramethyluroniumhexafluorophosphate (HATU), or the like) and non-nucleophilic base (e.g., triethylamine, *N*-methylmorpholine, and the like, or any suitable combination thereof) at

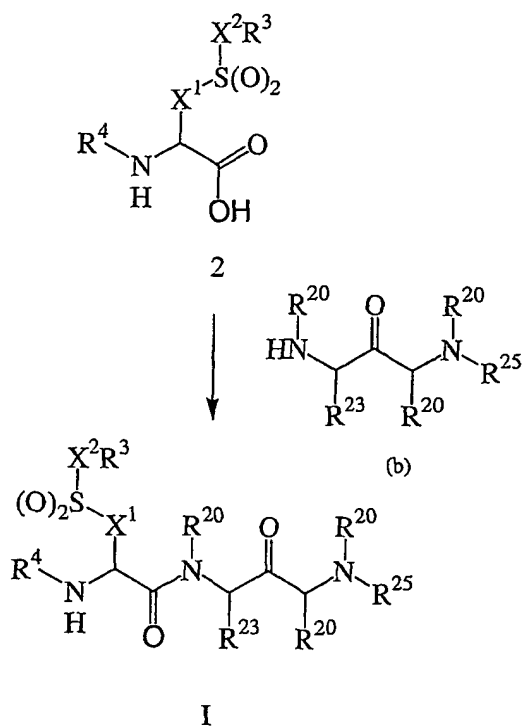
ambient temperature and requires 5 to 10 hours to complete.

An oxidation step, if required, can be carried out with an oxidizing agent (e.g., Oxone[®], metachloroperbenzoic acid or the like) in a suitable solvent (e.g., methanol, water, or the like, or any suitable combination thereof) at ambient temperature and requires 16 to 24 hours to complete. Detailed descriptions for the synthesis of a compound of Formula I by the processes in Reaction Scheme 1 are set forth in the Examples 1 to 11, *infra*.

Compounds of Formula I, where \dot{X}^3 is a compound of formula (b) (as defined in the Summary of the Invention), can be prepared by proceeding as in the following Reaction Scheme 2:

10

Reaction Scheme 2



in which each X^1 , X^2 , R^3 , R^4 , R^{20} , R^{23} and R^{25} are as defined for Formula I in the Summary of the Invention.

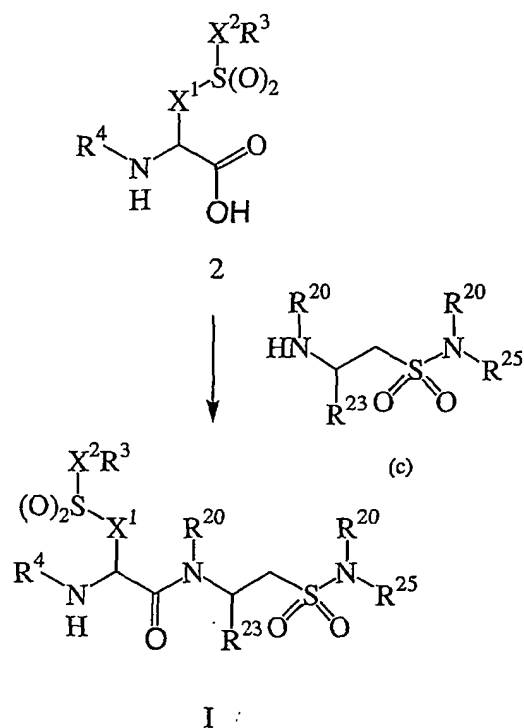
Compounds of Formula I can be prepared by condensing an acid of Formula 2 with an amino compound of formula (b). The condensation reaction can be effected with an appropriate coupling agent (e.g., benzotriazol-1-yloxytrispyrrolidinophosphonium hexafluorophosphate (PyBOP[®]), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI), *O*-benzotriazol-1-yl-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (HBTU), 1,3-dicyclohexylcarbodiimide (DCC), or the like) and optionally an appropriate catalyst (e.g., 1-hydroxybenzotriazole (HOBt), 1-hydroxy-7-azabenzotriazole (HOAt), *O*-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluroniumhexafluorophosphate (HATU), or the like) and non-nucleophilic base (e.g., triethylamine, *N*-methylmorpholine, and the like, or any suitable combination thereof) at ambient temperature and requires 5 to 10 hours to complete.

An oxidation step, if required, can be carried out with an oxidizing agent (e.g., Oxone[®], metachloroperbenzoic acid or the like) in a suitable solvent (e.g., methanol, water, or the like, or any suitable combination thereof) at ambient temperature and requires 16 to 24 hours to complete.

Compounds of Formula 1 in which X^3 is a compound of formula (c) (as defined in the Summary of the Invention), can be prepared by reacting a compound of Formula 2 with a compound of Formula (c) according to the following reaction scheme:

Reaction Scheme 3

-41-



in which each X^1 , X^2 , R^3 , R^4 , R^{20} , R^{23} and R^{25} are as defined for Formula I in the Summary of the Invention.

5

Additional Processes for Preparing Compounds of Formula I:

A compound of Formula I can be prepared as a pharmaceutically acceptable acid addition salt by reacting the free base form of the compound with a pharmaceutically acceptable inorganic or organic acid. Alternatively, a pharmaceutically acceptable base addition salt of a compound of Formula I can be prepared by reacting the free acid form of the compound with a pharmaceutically acceptable inorganic or organic base. Inorganic and organic acids and bases suitable for the preparation of the pharmaceutically acceptable salts of compounds of Formula I are set forth in the definitions section of this Application.

Alternatively, the salt forms of the compounds of Formula I can be prepared using salts of the starting materials or intermediates.

The free acid or free base forms of the compounds of Formula I can be prepared from the corresponding base addition salt or acid addition salt form. For example, a compound of Formula I in an acid addition salt form can be converted to the corresponding free base by treating with a suitable base (e.g., ammonium hydroxide solution, sodium hydroxide, and the like). A compound of Formula I in a base addition salt form can be converted to the corresponding free acid by treating with a suitable acid (e.g., hydrochloric acid, etc).

The *N*-oxides of compounds of Formula I can be prepared by methods known to those of ordinary skill in the art. For example, *N*-oxides can be prepared by treating an unoxidized form of the compound of Formula I with an oxidizing agent (e.g., trifluoroperacetic acid, permaleic acid, perbenzoic acid, peracetic acid, *meta*-chloroperoxybenzoic acid, or the like) in a suitable inert organic solvent (e.g., a halogenated hydrocarbon such as dichloromethane) at approximately 0°C. Alternatively, the *N*-oxides of the compounds of Formula I can be prepared from the *N*-oxide of an appropriate starting material.

Compounds of Formula I in unoxidized form can be prepared from *N*-oxides of compounds of Formula I by treating with a reducing agent (e.g., sulfur, sulfur dioxide, triphenyl phosphine, lithium borohydride, sodium borohydride, phosphorus trichloride, tribromide, or the like) in an suitable inert organic solvent (e.g., acetonitrile, ethanol, aqueous dioxane, or the like) at 0 to 80°C.

Prodrug derivatives of the compounds of Formula I can be prepared by methods known to those of ordinary skill in the art (e.g., for further details see Saulnier *et al.* (1994),

Bioorganic and Medicinal Chemistry Letters, Vol. 4, p. 1985). For example, appropriate prodrugs can be prepared by reacting a non-derivatized compound of Formula I with a suitable carbamylating agent (e.g., 1,1-acyloxyalkylcarbonochloridate, *para*-nitrophenyl carbonate, or the like).

5 Protected derivatives of the compounds of Formula I can be made by means known to those of ordinary skill in the art. A detailed description of the techniques applicable to the creation of protecting groups and their removal can be found in T.W. Greene, *Protecting Groups in Organic Synthesis*, 3rd edition, John Wiley & Sons, Inc. 1999.

Compounds of the present invention may be conveniently prepared, or formed during the

10 process of the invention, as solvates (e.g. hydrates). Hydrates of compounds of the present invention may be conveniently prepared by recrystallisation from an aqueous/organic solvent mixture, using organic solvents such as dioxin, tetrahydrofuran or methanol.

Compounds of Formula I can be prepared as their individual stereoisomers by reacting a racemic mixture of the compound with an optically active resolving agent to form a pair

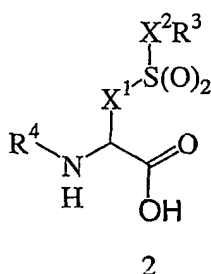
15 of diastereoisomeric compounds, separating the diastereomers and recovering the optically pure enantiomer. While resolution of enantiomers can be carried out using covalent diastereomeric derivatives of compounds of Formula I, dissociable complexes are preferred (e.g., crystalline diastereoisomeric salts). Diastereomers have distinct physical properties (e.g., melting points, boiling points, solubilities, reactivity, etc.) and can be readily

20 separated by taking advantage of these dissimilarities. The diastereomers can be separated by chromatography or, preferably, by separation/resolution techniques based upon differences in solubility. The optically pure enantiomer is then recovered, along with the resolving agent, by any practical means that would not result in racemization. A more detailed description of the techniques applicable to the resolution of stereoisomers of

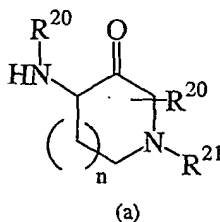
compounds from their racemic mixture can be found in Jean Jacques Andre Collet, Samuel H. Wilen, *Enantiomers, Racemates and Resolutions*, John Wiley & Sons, Inc. (1981).

In summary, the compounds of Formula I are made by a process which comprises:

- 5 (A) reacting a compound of Formula 2:



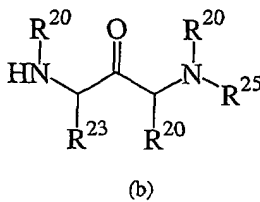
with a compound of the formula (a):



10

in which X^1 , X^2 , R^3 , R^4 , R^{20} and R^{21} are as defined in the Summary of the Invention for Formula I; or

- (B) reacting a compound of Formula 2 with a compound of the formula (b):

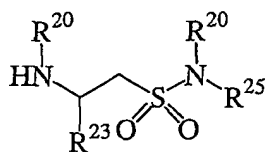


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in which R^{20} , R^{23} and R^{25} are as defined in the Summary of the Invention for Formula

I; or

(C) reacting a compound of Formula 2 with a compound of the formula (c):



(c)

5 in which R^{20} , R^{23} and R^{25} are as defined in the Summary of the Invention for Formula I; and

(D) optionally converting a compound of Formula I into a pharmaceutically acceptable salt;

10 (E) optionally converting a salt form of a compound of Formula I to non-salt form;

(F) optionally converting an unoxidized form of a compound of Formula I into a pharmaceutically acceptable *N*-oxide;

(G) optionally converting an *N*-oxide form of a compound of Formula I to its unoxidized form;

15 (H) optionally resolving an individual isomer of a compound of Formula I from a mixture of isomers;

(I) optionally converting a non-derivatized compound of Formula I into a pharmaceutically prodrug derivative; and

(J) optionally converting a prodrug derivative of a compound of Formula I to its
20 non-derivatized form.

Examples:

The present invention is further exemplified, but not limited by, the following examples that illustrate the preparation of compounds of Formula I (Examples) and
5 intermediates (References) according to the invention.

REFERENCE 1

3-amino-4-hydroxy-pyrrolidine-1-carboxylic acid tert-butyl ester

6-Oxa-3-aza-bicyclo[3.1.0]hexane-3-carboxylic acid tert-butyl ester (12.1g,
10 65.3mmol) was dissolved in a 8:1 methanol/water mixture (108mL). Ammonium chloride (15g) and sodium azide (21.4g, 329mmol) was added and the mixture was heated at 60°C overnight. After dilution with ether (500mL), the mixture was washed with saturated aqueous NaHCO₃ (200mL) and brine (200mL), dried with MgSO₄ and evaporated under vacuum. The crude product was dissolved in methanol (200mL). 10% Palladium on
15 activated carbon (1.5g) was added and the mixture was stirred at ambient temperature under a hydrogen atmosphere until TLC analysis showed the disappearance of the starting material. The mixture was filtered through a pad of Celite and evaporated to dryness under vacuum. The product was purified by flash chromatography on silica gel. Eluent: 5% methanol in ethyl acetate to 20% methanol, 3% triethylamine in ethyl acetate. Yield: 4.3g
20 3-amino-4-hydroxy-pyrrolidine-1-carboxylic acid tert-butyl ester as yellowish solid.

REFERENCE 2

4-Amino-3-hydroxy-azepane-1-carboxylic acid benzyl ester

Sodium hydride (60% in mineral oil, 10g, 250mmol) was suspended in dry DMF. Allyl-carbamic acid benzyl ester (19.1g, 100mmol) was added drop wise at ambient temperature. After stirring for 5 minutes, 5-bromo-1-pentene (25g, 168mmol) was added drop wise. Stirring was continued at 50°C for 1 hour. The reaction was quenched with
5 water and then partitioned between diethyl ether and water. The ether layer was washed with water and brine, dried with MgSO_4 and evaporated under vacuum. Flash chromatography (ethyl acetate/hexane 1:9) gave allyl-pent-4-enyl-carbamic acid benzyl ester (15.5g).

Allyl-pent-4-enyl-carbamic acid benzyl ester (15.5g, 59.8mmol) was dissolved in
10 dichloromethane and bis(tricyclohexylphosphine)benzylidene ruthenium(IV) dichloride (1g) was added. The mixture was refluxed under a nitrogen atmosphere until TLC analysis showed complete reaction. The solvent was evaporated under vacuum and the residue was purified by flash chromatography (ethyl acetate/hexane 1:9) to give 2,3,4,7-Tetrahydro-azepine-1-carboxylic acid benzyl ester (7.8g).

15 To a solution of 2,3,4,7-tetrahydro-azepine-1-carboxylic acid benzyl ester (4.5g, 19.45mmol) in dichloromethane (50mL) was added m-chloroperbenzoic acid (60mmol). The mixture was stirred at ambient temperature for 16 hours. Saturated aqueous K_2CO_3 solution was added and the mixture was extracted with dichloromethane. The combined organic layers were washed with saturated aqueous NaHCO_3 and brine, dried with MgSO_4
20 and evaporated under vacuum. The crude epoxide was dissolved in an 8:1 methanol/water mixture (100mL). Ammonium chloride (3.2g, 60mmol) and sodium azide (3.9g, 60mmol) were added and the mixture was heated at 60°C for 48 hours. Most of the solvent was removed under vacuum. The residue was extracted with ethyl acetate. The combined organic layers were washed with saturated aqueous NaHCO_3 (200mL) and brine (200mL),

dried with MgSO_4 and evaporated under vacuum. Flash chromatography of the residue (hexane/ethyl acetate 3:1) gave 4-azido-3-hydroxy-azepane-1-carboxylic acid benzyl ester (3.3g).

To a solution of 4-azido-3-hydroxy-azepane-1-carboxylic acid benzyl ester (3.3g, 11.37mmol) in methanol (50mL) was added triethylamine (5mL) and 1,3-propanedithiol (3.42mL, 35mmol). The mixture was stirred at ambient temperature until TLC analysis showed complete consumption of the starting material. A white precipitate was removed by filtration and the filtrate was evaporated to dryness. The residue was triturated with a 1:1 hexane/diethyl ether mixture to remove excess dithiol and dried under vacuum to yield 4-amino-3-hydroxy-azepane-1-carboxylic acid benzyl ester.

REFERENCE 3

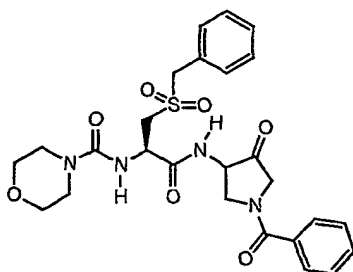
2S-Amino-N-(4-methoxyphenyl)-4-phenylbutane-1-sulfonamide hydrochloride

A solution comprised of crude *tert*-butyl 1-(4-methoxyphenylsulfamoylmethyl)-3-phenylpropylcarbamate (1.92 g, 4.42 mmol), prepared as in Reference Example 2, in DCM (10 mL) was treated with a 4M solution of hydrogen chloride in dioxane (11 mL). The mixture was stirred for 16 hours at room temperature and diluted with diethyl ether. A resulting precipitate was collected by filtration, washed several times with diethyl ether and hexane and pumped dry to provide 2S-amino-N-4-methoxyphenyl-4-phenylbutane-1-sulfonamide hydrochloride with quantitative mass recovery. ^1H NMR (DMSO): 2.05 (2H, m); 2.6-2.7 (2H, m); 3.4 (3H, m*); 3.72 (3H, s); 6.9 (2H, d, $J=7$ Hz); 7.25 (5H, m); 7.3 (2H, d, $J=7$ Hz); 8.5 (br. s); 10.0 (1H, s).

EXAMPLE 1

Morpholine-4-carboxylic acid [1-(1-benzoyl-4-oxo-pyrrolidin-3-ylcarbamoyl)-2-phenylmethanesulfonyl-ethyl]-amide

(Compound 1)



5 2-[(Morpholine-4-carbonyl)-amino]-3-phenylmethanesulfonyl-propionic acid (1g, 2.8mmol), 3-amino-4-hydroxy-pyrrolidine-1-carboxylic acid tert-butyl ester (700mg, 3.46mmol) prepared as in Reference 1, EDC (1.5g, 7.8mmol), and HOBt (1.5g, 9.6mmol) were combined. Dichloromethane (10mL) was added and then 4-methylmorpholine (1.5mL). The mixture was stirred at ambient temperature for 2 hours. After dilution with
10 ethyl acetate (200mL) the solution was washed with saturated aqueous NaHCO₃ (100mL) and brine (100mL), dried with MgSO₄ and evaporated under vacuum. 3-Hydroxy-4-{2-[(morpholine-4-carbonyl)-amino]-3-phenylmethanesulfonyl-propionylamino}-pyrrolidine-1-carboxylic acid tert-butyl ester (1.05g, 1.94mmol) was obtained as yellowish foam and was dissolved in dichloromethane (6mL). Trifluoroacetic acid (6mL) was added and the
15 mixture was stirred at ambient temperature for 1 hour. Evaporation under vacuum gave crude morpholine-4-carboxylic acid [1-(4-hydroxy-pyrrolidin-3-ylcarbamoyl)-2-phenylmethanesulfonyl-ethyl]-amide as TFA salt, which was used without further purification.

 Morpholine-4-carboxylic acid [1-(4-hydroxy-pyrrolidin-3-ylcarbamoyl)-2-phenylmethanesulfonyl-ethyl]-amide TFA salt (215mg, 0.39mmol) was dissolved in 1,4-
20

dioxane (20mL). Saturated aqueous NaHCO₃ solution (10mL) was added followed by benzoyl chloride (0.2mL, 1.72mmol). The mixture was stirred at ambient temperature for 1 hour and then extracted with ethyl acetate. The combined organic layers were washed with saturated aqueous NaHCO₃ and brine, dried with MgSO₄ and evaporated under vacuum. The residue was purified by flash chromatography on silica gel (Eluent: 5% methanol in ethyl acetate to 20% methanol in ethyl acetate) to yield morpholine-4-carboxylic acid [1-(1-benzoyl-4-hydroxy-pyrrolidin-3-ylcarbamoyl)-2-phenylmethanesulfonyl-ethyl]-amide (92mg).

Morpholine-4-carboxylic acid [1-(1-benzoyl-4-hydroxy-pyrrolidin-3-ylcarbamoyl)-2-phenylmethanesulfonyl-ethyl]-amide (92mg, 0.169mmol) was dissolved in DMSO (5mL). Triethylamine (0.5mL) and then SO₃ pyridine complex (150mg) were added and the mixture was stirred at ambient temperature for 3 hours. After dilution with ethyl acetate (100mL), the solution was washed with water (50mL) and brine, dried with MgSO₄ and evaporated under vacuum. The residue was purified by flash chromatography on silica gel (Eluent: 5% methanol in ethyl acetate) to yield morpholine-4-carboxylic acid [1-(1-benzoyl-4-oxo-pyrrolidin-3-ylcarbamoyl)-2-phenylmethanesulfonyl-ethyl]-amide as a mixture of diastereomers (Yellowish solid; 38mg); ¹H NMR: (DMSO) 8.50-8.35 (m, 1H), 7.55-7.34 (m, 10H), 7.16-6.95 (m, 1H), 4.80-4.65 (m, 1H), 4.54-4.22 (m, 3H), 3.98-3.25 (m, 14H); MS: (M+H)⁺ 543.

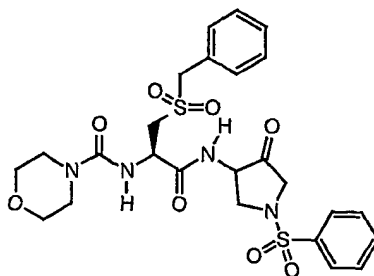
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EXAMPLE 2

Morpholine-4-carboxylic acid [1-(1-benzenesulfonyl-4-oxo-pyrrolidin-3-ylcarbamoyl)-2-phenylmethanesulfonyl-ethyl]-amide

(Compound 2)

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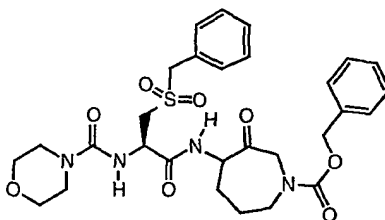


Morpholine-4-carboxylic acid [1-(1-benzenesulfonyl-4-oxo-pyrrolidin-3-ylcarbamoyl) 2-phenylmethanesulfonyl-ethyl]-amide was prepared following the procedure detailed in Example 1, substituting benzenesulfonyl chloride for benzoyl chloride; ¹H NMR: (DMSO) [8.35 (d, J=7.4Hz), 8.28 (d, J=7.6Hz), 1H], 7.87-7.62 (m, 5H), 7.41-7.32 (m, 5H), 7.06-6.98 (m, 1H), 4.72-4.60 (m, 1H), 4.45 (s, 2H), 4.42-4.23 (m, 1H), 3.92-3.79 (m, 2H), 3.55-3.20 (m, 11H), 3.06-2.97 (m, 1H). MS: (M+H)⁺ 579.

EXAMPLE 3

10 4-{2-[(Morpholine-4-carbonyl)-amino]-3-phenylmethanesulfonyl-propionylamino}-3-oxo-azepane-1-carboxylic acid benzyl ester

(Compound 3)



Crude 4-amino-3-hydroxy-azepane-1-carboxylic acid benzyl ester (150mg, 0.57mmol) prepared as in Reference 2, 2-[(morpholine-4-carbonyl)-amino]-3-phenylmethanesulfonyl-propionic acid (400mg, 1.12mmol), EDC (400mg, 2.1mmol), and HOBt (400mg, 2.5mmol) were combined. Dichloromethane (10mL) was added followed

by 4-methylmorpholine (0.5mL). The mixture was stirred at ambient temperature for 2 hours. After dilution with ethyl acetate (100mL) the solution was washed with 1N HCl, saturated aqueous NaHCO₃ and brine, dried with MgSO₄ and evaporated under vacuum. The residue was purified by flash chromatography (ethyl acetate/methanol 9:1) to yield 3-hydroxy-4-{2-[(morpholine-4-carbonyl)-amino]-3-phenylmethanesulfonyl-propionyl-amino}-azepane-1-carboxylic acid benzyl ester (320mg).

3-Hydroxy-4-{2-[(morpholine-4-carbonyl)-amino]-3-phenylmethanesulfonyl-propionylamino}-azepane-1-carboxylic acid benzyl ester (100mg, 0.167mmol) was dissolved in DMSO (5mL). Triethylamine (0.3mL) and then SO₃ pyridine complex (150mg) were added and the mixture was stirred at ambient temperature for 3 hours. After dilution with ethyl acetate (100mL), the solution was washed with water (50mL) and brine, dried with MgSO₄ and evaporated under vacuum. The residue was purified by flash chromatography on silica gel (Eluent: 5% methanol in ethyl acetate) to yield 4-{2-[(morpholine-4-carbonyl)-amino]-3-phenylmethanesulfonyl-propionylamino}-3-oxo-
azepane-1-carboxylic acid benzyl ester (75mg); ¹H NMR: (DMSO) 8.23-8.08 (m, 1H), 7.40-7.29 (m, 10H), 7.06-6.98 (m, 1H), 5.20-5.09 (m, 2H), 4.79-4.65 (m, 1H), 4.52-4.31 (m, 3H), 4.02-3.80 (m, 2H), 3.62-3.23 (m, 11H), 3.00-2.78 (m, 1H), 1.88-1.55 (m, 4H); MS: (M+H)⁺ 601.

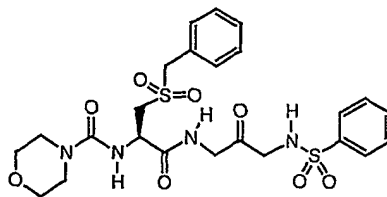
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EXAMPLE 4

Morpholine-4-carboxylic acid [1-(3-benzenesulfonylamino-2-oxo-propylcarbamoyl)-2-phenylmethanesulfonyl-ethyl]-amide

(Compound 4)

-53-



N-(3-Amino-2-hydroxy-propyl)-benzenesulfonamide TFA salt was prepared as outlined in Renee L. DesJarlais et al. *J. Am. Chem. Soc.* **1998**, *120*, 9114-9115.

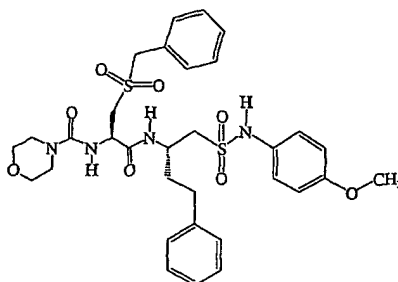
2-[(Morpholine-4-carbonyl)-amino]-3-phenylmethanesulfonyl-propionic acid
 5 (50mg, 0.14mmol), *N*-(3-amino-2-hydroxy-propyl)-benzenesulfonamide TFA salt (60mg, 0.17mmol), EDC (100mg, 0.52mmol), and HOBT (100mg, 0.64mmol) were combined. DMF (3mL) was added and then 4-methylmorpholine (0.3mL). The mixture was stirred at ambient temperature for 3 hours. After dilution with ethyl acetate (100mL) the solution was washed with 1N HCl, saturated aqueous NaHCO₃ and brine, dried with MgSO₄ and
 10 evaporated under vacuum. The residue was dissolved in acetone (5mL). Jones reagent was added until the orange color persisted. The mixture was stirred for 2 hours, quenched with isopropanol, and diluted with ethyl acetate (100mL). The solution was washed with water, saturated aqueous NaHCO₃ and brine, dried with MgSO₄ and evaporated under vacuum. The crude product was recrystallized from ethyl acetate/diethyl ether to give
 15 morpholine-4-carboxylic acid [1-(3-benzenesulfonylamino-2-oxo-propylcarbamoyl)-2-phenylmethanesulfonyl-ethyl]-amide as white solid (19mg); ¹H NMR: (DMSO) 8.17 (t, J=5.7Hz, 1H), 7.93 (t, J=5.9Hz, 1H), 7.76-7.48 (m, 5H), 7.36-7.29 (m, 5H), 7.05 (d, J=8.1Hz, 1H), 4.68-4.59 (m, 1H), 4.45 (s, 2H), 3.89 (d, J=5.7Hz, 2H), 3.79-3.75 (m, 2H), 3.56-3.22 (m, 10H); MS: (M+H)⁺ 567.

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EXAMPLE 5

N-{1*S*-[1*S*-(4-Methoxyphenylsulfamoylmethyl)-3-phenylpropylcarbamoyl] 2-benzylsulfonylethyl}-morpholine-4-carboxamide

(Compound 7)



5 A mixture comprised of 2*S*-morpholin-4-ylcarbonylamino-3-benzylsulfonyl-propionic acid (0.194 g, 0.599 mmol), 2*S*-amino-*N*-(4-methoxyphenyl)-4-phenylbutane-1-sulfonamide hydrochloride (0.222 g, 0.599 mmol), prepared as in Reference 3, and HATU (0.228 g, 0.599 mmol) in DMF (5 mL) was treated with 4-methylmorpholine (0.198 g, 1.80 mmol). The mixture was stirred at room temperature for approximately 12 hours and then

10 partitioned among a 4:1:2:3 mixture (100 mL total) of ethyl acetate, THF, water, and brine, respectively. The organic phase was separated and washed with saturated aqueous sodium bicarbonate (30 mL), brine (30 mL), dried (MgSO₄), filtered and concentrated. The residue was triturated with of 5:1 ether/ethyl acetate (100 mL), collected by filtration, washed with ether (30 mL), hexane (30 mL), and pumped dry to provide *N*-{1*S*-[1*S*-(4-

15 methoxyphenylsulfamoylmethyl)-3-phenylpropylcarbamoyl]-2-benzylsulfonylethyl}-
morpholine-4-carboxamide. TLC R_f (ethyl acetate): 0.65; ¹H NMR (DMSO): 1.74 (1H, m); 1.92 (1H, m); 2.39-2.61 (2H, m); 3.1-3.35 (2H, 2xddd*); 3.34 (4H, m); 3.42-3.65 (6H, m*); 3.72 (3H, s); 4.24 (1H, m); 4.51 (2H, s); 4.61 (1H, m); 6.88 (2H, d, J=9 Hz); 7.1-7.34 (8H, m); 7.4 (5H, s); 8.12 (1H, d, J=8.7 Hz); MS (M+1): 673.

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Proceeding as in Example 5 the following compounds of Formula I were prepared:

N-{1S-[5-amino-1S-(4-methoxyphenyl)sulfamoyl-methyl]pentylcarbamoyl}-2-benzylsulfonyl-ethyl-morpholine-4-carboxamide hydrobromide (Compound 5); ¹H NMR (DMSO): 1.15-1.73 (6H, m*); 2.71 (2H, m); 3.05-3.25 (2H, 2xdd); 3.37 (4H, m); 3.45-3.6 (6H, m*); 3.72 (3H, s); 4.21 (1H, m); 4.49 (2H, dd); 4.5 (1H, m*); 6.89 (2H, d, J=8.9 Hz); 7.09 (1H, m*); 7.15 (2H, d, J=8.9 Hz); 7.39 (5H, s); 7.73 (3H, br. s); 8.03 (1H, d, J=8.6 Hz); 9.47 (1H, s); MS (M+1): 640, free base); and

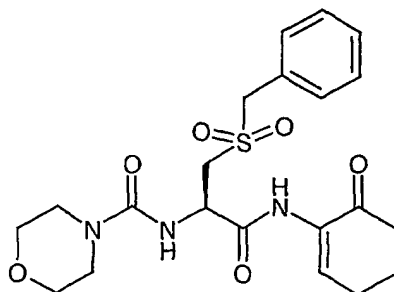
Benzyl 6-(4-methoxyphenylsulfamoyl)-5S-(2S-morpholin-4-ylcarbonylamino-3-benzylsulfonyl-propionylamino)hexylcarbamate (Compound 6); TLC R_f (ethyl acetate): 0.3; ¹H NMR (DMSO): 1.1-1.65 (6H, m); 2.94 (2H, q, J=6 Hz); 3.05-3.22 (2H, 2xdd); 3.34 (4H, m*); 3.35-3.59 (2H, m*); 3.53 (4H, br s); 3.71 (3H, s); 4.19 (1H, m*); 4.53 (2H, dd, J=15 Hz); 4.57 (1H, m*); 5.00 (2H, s); 6.89 (2H, d, J=8.4 Hz); 7.05 (1H, d, J=8 Hz); 7.15 (2H, d, J=8.4 Hz); 7.24 (1H, t); 7.3-7.45 (10H, 2xs); 7.99 (1H, J=8 Hz); MS (M+): 774.

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EXAMPLE 6

Morpholine-4-carboxylic acid [(R)-1-(6-oxo-cyclohex-1-enylcarbamoyl)-2-phenylmethanesulfonyl-ethyl]-amide

(Compound 8)



20

A solution of 2-amino-cyclohexane-1,3-diol (0.55 g) in dimethylformamide (30ml) was treated with diisopropylethylamine (1.6ml, 9.2mmol). After stirring at room temperature for 5 minutes the mixture was treated with (R)-2-[(morpholine-4-carbonyl)-amino]-3-phenylmethanesulfonyl-propionic acid (1.73g, 4.86mmol) followed by HATU (1.68g, 4.42mmol). This mixture was stirred at room temperature overnight and then evaporated. The residue was subjected to flash chromatography on silica eluting with ethyl acetate and then a mixture of ethyl acetate and methanol to give morpholine-4-carboxylic acid [(R)-1-(2,6-dihydroxy-cyclohexylcarbamoyl)-2-phenylmethanesulfonyl-ethyl]-amide as a white solid (210mg). MS: 470 (MH⁺).

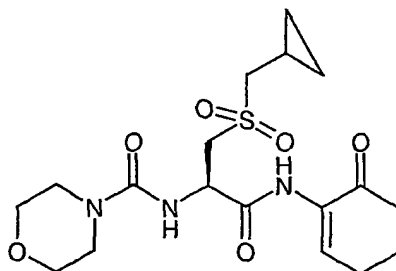
10 A solution of morpholine-4-carboxylic acid [(R)-1-(2,6-dihydroxy-cyclohexylcarbamoyl)-2-phenylmethanesulfonyl-ethyl]-amide (90mg, 0.19mmol) in methylene chloride (6ml) was treated with Dess-Martin periodinane (162mg, 0.38mmol). After stirring at room temperature for 2 hours the reaction mixture was washed with a solution of Na₂S₂O₃ in water (0.26M), then with saturated aqueous bicarbonate solution
15 then with water, then dried over Na₂SO₄ and then evaporated under reduced pressure. The residue was subjected to flash chromatography on silica eluting with a mixture of ethyl acetate and heptane to give morpholine-4-carboxylic acid [(R)-1-(6-oxo-cyclohex-1-enylcarbamoyl)-2-phenylmethanesulfonyl-ethyl]-amide (8mg). ¹H NMR (CDCl₃) : 9.00 (s, 1H), 7.82 (t, J=5Hz, 1H), 7.53-7.38 (m, 5H), 6.06 (d, J=6Hz, 1H), 5.00 (m, 1H), 4.47-
20 4.27 (m, 2H), 3.85 (m, 1H), 3.77-3.62 (m, 4H), 3.48-3.36 (m, 4H), 3.27 (m, 1H), 2.58-2.46 (m, 4H), 2.08-1.97 (m, 2H). MS: 450 (MH⁺).

EXAMPLE 7

Morpholine-4-carboxylic acid [(R)-2-cyclopropylmethanesulfonyl-1-(6-oxo-cyclohex-1-enylcarbamoyl)-ethyl]-amide

5

(Compound 9)



A mixture of (R)-3-cyclopropylmethanesulfonyl-2-[(morpholine-4-carbonyl)-amino]-propionic acid (0.352g, 1.1 mmol) and N-cyclohexylcarbodiimide N'-methylpolystyrene (1.93 mmol/g, 1.03g) in DCM (10mL) was treated with
10 hydroxybenzotriazole (0.27g, 2 mmol). After stirring at room temperature for 5 minutes the mixture was treated with 2-amino-cyclohexane-1,3-diol (0.0131g, 1 mmol) and stirring was continued for a further 2 days. The reaction mixture was treated with PS Trisamine (3.75 mmol/g, 1.3g) and after stirring at room temperature for 2 hours the resin was filtered off and washed with DCM. The combined filtrate plus washings were evaporated under
15 reduced pressure to give morpholine-4-carboxylic acid [(R)-2-cyclopropylmethanesulfonyl-1-(2,6-dihydroxy-cyclohexylcarbamoyl)-ethyl]-amide (0.32g) as pale yellow thick oil. MS: 434 (MH⁺).

Dess Martin Periodinane (0.688 g, 1.62 mmol) was added to a solution of the [(R)-2-cyclopropylmethanesulfonyl-1-(2,6-dihydroxy-cyclohexylcarbamoyl)-ethyl]-amide
20 (0.32g) in DCM (10mL) and the mixture was stirred at room temperature for 3 hours then

treated with resin bound $\text{Na}_2\text{S}_2\text{O}_3$ (1.5 mmol/g, 1.9g) and stirred at room temperature for a further 24 hours. The reaction mixture was diluted with DCM (20mL) , then filtered. The filtrate was washed with a solution of 0.25 M $\text{Na}_2\text{S}_2\text{O}_3$, then with saturated NaHCO_3 , then dried (MgSO_4), and then evaporated under reduced pressure. The residue was

5 subjected to column chromatography eluting with a mixture of ethyl acetate and heptane to give morpholine-4-carboxylic acid [(R)-2-cyclopropylmethanesulfonyl-1-(6-oxo-cyclohex-1-enylcarbamoyl)-ethyl]-amide. ^1H NMR (CDCl_3): 9.00 (s, 1H), 7.78 (t, 1H), 6.18 (d, 1H), 4.9 (m, 1H), 3.85 (m, 1H), 3.77-3.62 (m, 4H), 3.58-3.45 (dd, 1H), 3.48-3.36 (m, 4H), 3.0 (d, 2H), 2.55-2.42 (m, 4H), 2.08-1.97 (m, 2H), 1.2 (m, 1H), 0.8-0.7 (m, 2H),

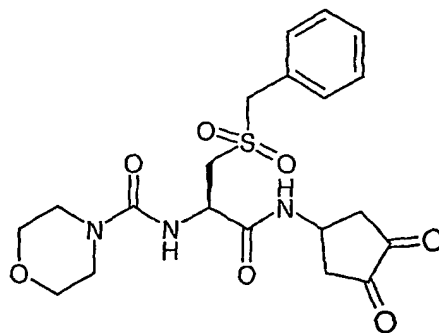
10 0.6-0.4 (m, 2H). MS: 414 (MH^+).

EXAMPLE 8

Morpholine-4-carboxylic acid [(R)-1-(3,4-dioxo-cyclopentylcarbamoyl)-2-phenylmethanesulfonyl-ethyl]-amide

15

(Compound 10)



A solution of 4-amino-cyclopentane-1, 2-diol; compound with trifluoroacetic acid (745mg, 3.23mmol) in DMF (15ml) was treated with DIPEA (1.12ml, 6.4mmol) and the mixture was stirred for 5 minutes at room temperature. Then (R)-2-[(Morpholine-4-

carbonyl)-amino]-3-phenylmethanesulfonyl-propionic acid (1.15g, 3.23mmol) was added followed by HATU (1.23g, 3.24mmol). This mixture was stirred at room temperature overnight and then evaporated. The residue was subjected to flash chromatography on silica eluting with ethyl acetate and then with a mixture of ethyl acetate and methanol to
5 give morpholine-4-carboxylic acid [(R)-1-(3,4-dihydroxy-cyclopentylcarbamoyl)-2-phenylmethanesulfonyl-ethyl]-amide as a brown solid (680mg). LC/MS: RT=2.64min. (215 and 254nM), MH^+ =456.

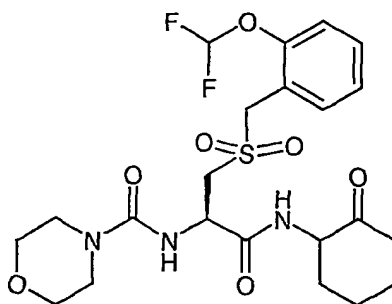
A solution of morpholine-4-carboxylic acid [(R)-1-(3,4-dihydroxy-cyclopentylcarbamoyl)-2-phenylmethanesulfonyl-ethyl]-amide (670mg, 1.47mmol) in
10 methylene chloride (40ml) was treated with Dess-Martin periodinane (624mg, 1.47mmol) and the reaction stirred at room temperature overnight. More Dess-Martin periodinane (642mg, 1.51mmol) was added and the reaction stirred at room temperature for 6hours and then overnight. The reaction mixture was washed with a solution of $Na_2S_2O_3$ in water (0.26M), then with saturated aqueous bicarbonate solution, then with water, then dried
15 over Na_2SO_4 and then evaporated under reduced pressure. The residue was subjected to flash chromatography on silica eluting with a mixture of ethyl acetate and heptane, then with ethyl acetate to give morpholine-4-carboxylic acid [(R)-1-(3,4-dioxo-cyclopentylcarbamoyl)-2-phenylmethanesulfonyl-ethyl]-amide as an off white solid (45mg). 1H NMR ($CDCl_3$): 7.50-7.38 (m, 5H), 6.62 (m, 1H), 5.91 (d, J=5Hz, 1H), 4.81
20 (m, 1H), 4.58-4.35 (m, 3H), 3.73-3.61 (m, 5H), 3.44-3.32 (m, 4H), 3.22 (m, 1H), 2.72-2.12 (m, 4H). MS: 452 (MH^+).

EXAMPLE 9

Morpholine-4-carboxylic acid [2-(2-difluoromethoxy-phenylmethanesulfonyl)-1-(2-

oxo-cyclohexylcarbamoyl)-ethyl]-amide

(Compound 11)



5 3-(2-Difluoromethoxy-phenylmethanesulfonyl)-2-[(morpholine-4-carbonyl)-
amino]-propionic acid (100mg, 0.237mmol), 2-aminocyclohexanol (58mg, 0.5mmol), EDC
(100mg, 0.52mmol), and HOBt (100mg, 0.64mmol) were combined. Dichloromethane
(2mL) was added and then 4-methylmorpholine (0.2mL). The mixture was stirred at
ambient temperature for 2h. After dilution with ethyl acetate (100mL) the solution was
10 washed with 1N aqu. HCl (30mL), sat. aqu. NaHCO₃ (30mL) and brine (30mL), dried with
MgSO₄ and evaporated under vacuum. The crude product was dissolved in
dichloromethane (10mL). Dess-Martin periodinane (300mg, 0.71mmol) was added, and
the reaction mixture was stirred at ambient temperature for 1h. After dilution with ethyl
acetate (100mL), the solution was washed with 0.26M Na₂S₂O₃ in sat. aqu. NaHCO₃
15 (30mL), sat. aqu. NaHCO₃ and brine, dried with MgSO₄, and evaporated under vacuum.
Purification by flash-chromatography on silica gel (ethyl acetate/hexane) gave morpholine-
4-carboxylic acid [2-(2-difluoromethoxy-phenylmethanesulfonyl)-1-(2-oxo-
cyclohexylcarbamoyl)-ethyl]-amide (78mg, 0.151mmol) as a white solid. Mixture of
diastereomers: ¹H NMR: (DMSO) [8.03 (d, J=7.2Hz), 7.96 (d, J=7.2Hz), 1H], 7.50-7.42
20 (m, 2H), 7.30-7.21 (m, 2H), 7.10 (t, J_{H,F}=74Hz, 1H), 7.03 (d, J=8.4Hz, 1H), 4.78-4.69 (m,

1H), 4.54 (s, 2H), 4.41-4.33 (m, 1H), 3.62-3.25 (m, 10H), 2.55-1.40 (m, 8H). MS: (M+H)⁺ 518.

By proceeding in similar manner to Example 9 but using 2-aminocyclopentanol
5 there was prepared morpholine-4-carboxylic acid [2-(2-difluoromethoxy-phenylmethanesulfonyl)-1-(2-oxo-cyclopentylcarbamoyl)-ethyl]-amide (Compound 12)
as a mixture of diastereomers: ¹H NMR: (DMSO) [8.19 (d, J=8Hz), 7.15 (d, J=8Hz),
1H], 7.49-7.42 (m, 2H), 7.30-7.21 (m, 2H), 7.10 (t, J_{H,F}=74Hz, 1H), [7.02 (d, J=8.4Hz),
7.00 (d, J=8.4Hz), 1H], 4.77-4.70 (m, 1H), [4.53 (s), 4.52 (s), 2H], 4.10-3.91 (m, 1H),
10 3.60-3.23 (m, 10H), 2.28-1.70 (m, 6H). MS: (M+H)⁺ 504.

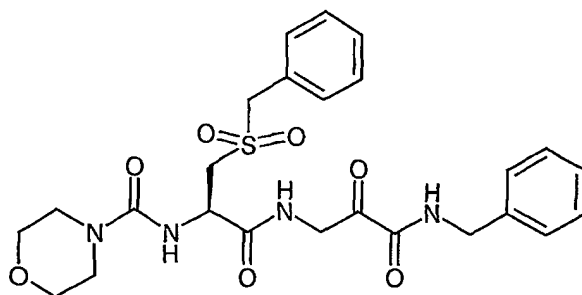
By proceeding in similar manner to Example 9 but using 2-aminocyclobutanol
there was prepared morpholine-4-carboxylic acid [2-(2-difluoromethoxy-phenylmethanesulfonyl)-1-(2-oxo-cyclobutylcarbamoyl)-ethyl]-amide (Compound 13)
15 as a mixture of diastereomers: ¹H NMR: (DMSO) 8.49 (d, J=7.6Hz, 1H), 7.48-7.42 (m,
2H), 7.30-7.21 (m, 2H), 7.11 (t, J_{H,F}=74Hz, 1H), 7.02 (d, J=8.8Hz, 1H), 4.88-4.67 (m,
2H), 4.53 (s, 2H), 3.64-3.23 (m, 10H), 2.93-2.70 (m, 2H), 2.23-1.99 (m, 2H). MS:
(M+H)⁺

20

EXAMPLE 10

(Morpholine-4-carboxylic acid [1-(2-benzylcarbamoyl-2-oxo-ethylcarbamoyl)-2-phenylmethanesulfonyl-ethyl]-amide)

(Compound 14)



Isoserine (3.11g, 29.6mmol) was dissolved in 1,4-dioxane/H₂O 3:1 (40mL). K₂CO₃ (0.5g) and NaHCO₃ (0.5g) was added. Di-*tert*-butyl dicarbonate (6.45g, 29.6mmol) was added and the mixture was stirred at ambient temperature over night. The reaction mixture
 5 was extracted with dichloromethane (3x100mL). The combined organic phases were washed with brine, dried with MgSO₄, and evaporated under vacuum. The crude 3-*tert*-butoxycarbonylamino-2-hydroxy-propionic acid (4.76g, 23.2mmol) was obtained as a colorless oil, which solidified on standing, and was used without further purification.

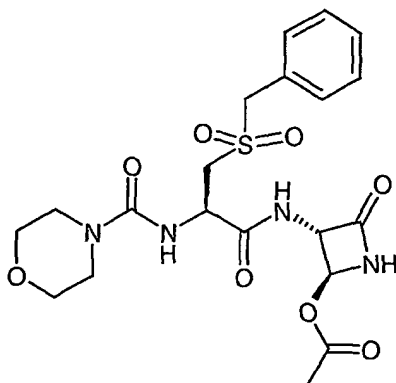
10 3-*tert*-butoxycarbonylamino-2-hydroxy-propionic acid (1.5g, 7.31mmol), benzylamine (1.1mL, 10.0mmol), EDC (2.5g, 13.1mmol), and HOBt (2.0g, 12.8mmol) were combined. Dichloromethane (15mL) was added and then 4-methylmorpholine (2mL). The mixture was stirred at ambient temperature for 2h. After dilution with ethyl acetate (300mL) the solution was washed with 1N aqu. HCl (100mL), sat. aqu. NaHCO₃
 15 (100mL) and brine (100mL), dried with MgSO₄ and evaporated under vacuum. Yield: 1.83g, 6.22mmol (2-Benzylcarbamoyl-2-hydroxy-ethyl)-carbamic acid *tert*-butyl ester.

(2-Benzylcarbamoyl-2-hydroxy-ethyl)-carbamic acid *tert*-butyl ester (0.2g, 0.68mmol) was dissolved in dichloromethane (2mL) and trifluoroacetic acid (2mL). After
 20 stirring for 2h at ambient temperature, the solution was evaporated under vacuum and the

- residue was dried under high vacuum. To this residue were added EDC (200mg, 1.05mmol), HOBt (200mg, 1.28mmol), 2-[(Morpholine-4-carbonyl)-amino]-3-phenylmethanesulfonyl-propionic acid (200mg, 0.56mmol), dichloromethane (5mL) and 4-methylmorpholine (0.5mL). The mixture was stirred at ambient temperature for 2h.
- 5 After dilution with ethyl acetate (100mL) the solution was washed with 1N aqu. HCl (30mL), sat. aqu. NaHCO₃ (30mL) and brine (30mL), dried with MgSO₄ and evaporated under vacuum. The crude product was dissolved in dichloromethane (10mL). Dess-Martin periodinane (500mg, 1.18mmol) was added, and the reaction mixture was stirred at ambient temperature for 1h. After dilution with ethyl acetate (100mL), the solution was
- 10 washed with 0.26M Na₂S₂O₃ in sat. aqu. NaHCO₃ (30mL), sat. aqu. NaHCO₃ and brine, dried with MgSO₄, and evaporated under vacuum. The product (morpholine-4-carboxylic acid [1-(2-benzylcarbamoyl-2-oxo-ethylcarbamoyl)-2-phenylmethanesulfonyl-ethyl]-amide) was crystallized from ethyl acetate/diethylether and was obtained as a white solid (153mg, 0.29mmol). ¹H NMR: (DMSO) 9.24 (t, J=6.4Hz, 1H), 8.19 (t, J=5.6Hz, 1H),
- 15 7.39-7.19 (m, 10H), 7.08 (d, J=8Hz, 1H), 4.83-4.76 (m, 1H), 4.49 (s, 2H), 4.48-4.33 (m, 2H), 4.31 (d, J=6.8Hz, 2H), 3.68-3.25 (m, 10H). MS: (M+H)⁺ 531.

EXAMPLE 11

- Acetic acid 3-{2-[(morpholine-4-carbonyl)-amino]-3-phenylmethanesulfonyl-
20 propionylamino}-4-oxo-azetidin-2-yl ester
- (Compound 15)



Acetic acid 3-benzyloxycarbonylamino-4-oxo-azetidin-2-yl ester was prepared as outlined in J.C. Arnould et al. *Eur. J. Med. Chem* **1992**, 27, 131-140.

5 Acetic acid 3-benzyloxycarbonylamino-4-oxo-azetidin-2-yl ester (100mg, 0.36mmol) was hydrogenated on a Parr shaker over 10% palladium on carbon (100mg) in ethyl acetate (20mL) at 50 psi for 5h. The mixture was filtered through Celite and evaporated. Acetic acid 3-amino-4-oxo-azetidin-2-yl ester was obtained in quantitative yield.

10

2-[(Morpholine-4-carbonyl)-amino]-3-phenylmethanesulfonyl-propionic acid (100mg, 0.28mmol), acetic acid 3-amino-4-oxo-azetidin-2-yl ester (52mg, 0.36mmol), EDC (100mg, 0.52mmol), and HOBt (100mg, 0.64mmol) were combined. Dichloromethane (2mL) was added and then 4-methylmorpholine (0.2mL). The mixture
 15 was stirred at ambient temperature for 2h. After dilution with ethyl acetate (100mL) the solution was washed with 1N aqu. HCl (30mL), sat. aqu. NaHCO₃ (30mL) and brine (30mL), dried with MgSO₄ and evaporated under vacuum. The residue was subjected to flash chromatography on silica gel (ethyl acetate) to give acetic acid 3-{2-[(morpholine-4-

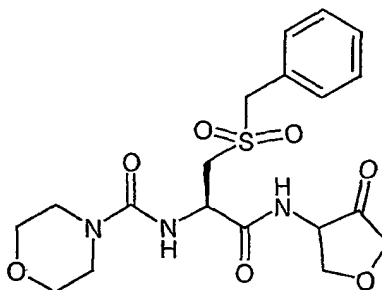
carbonyl)-amino]-3-phenylmethanesulfonyl-propionylamino}-4-oxo-azetidin-2-yl ester
 (17mg, 0.035mmol). ^1H NMR: (DMSO) 9.18 (s, 1H), 8.72 (d, $J=6.4\text{Hz}$, 1H), 7.41-7.30
 (m, 5H), 7.08 (m, 1H), 5.76 (s, 1H), 4.80-4.61 (m, 2H), 4.49 (s, 2H), 3.63-3.22 (m, 10H),
 2.08 (s, 3H). MS: $(\text{M}+\text{H})^+$ 483.

5

EXAMPLE 12

Morpholine-4-carboxylic acid [1-(4-oxo-tetrahydro-furan-3-ylcarbamoyl)-2-
phenylmethanesulfonyl-ethyl]-amide

(Compound 16)



10

4-Amino-tetrahydro-furan-3-ol was prepared as outlined in Marquis, Robert W. et
 al. *J. Med. Chem* **2001**, 44, 725-736.

2-[(Morpholine-4-carbonyl)-amino]-3-phenylmethanesulfonyl-propionic acid
 15 (100mg, 0.28mmol), 4-aminotetrahydrofuran-3-ol (100mg, 0.96mmol), EDC (200mg,
 1.04mmol), and HOBT (200mg, 1.28mmol) were combined. DMF (2mL) was added and
 then 4-methylmorpholine (0.2mL). The mixture was stirred at ambient temperature for 2h.
 After dilution with ethyl acetate (100mL) the solution was washed with 1N aq. HCl
 (30mL), sat. aq. NaHCO_3 (30mL) and brine (30mL), dried with MgSO_4 and evaporated
 20 under vacuum. The crude product was dissolved in dichloromethane (10mL). Dess-Martin

periodinane (300mg, 0.71mmol) was added, and the reaction mixture was stirred at ambient temperature for 1h. After dilution with ethyl acetate (100mL), the solution was washed with 0.26M Na₂S₂O₃ in sat. aqu. NaHCO₃ (30mL), sat. aqu. NaHCO₃ and brine, dried with MgSO₄, and evaporated under vacuum. Purification by flash-chromatography on silica gel (ethyl acetate) gave morpholine-4-carboxylic acid [1-(4-oxo-tetrahydro-furan-3-ylcarbamoyl)-2-phenylmethanesulfonyl-ethyl]-amide (8.6mg, 0.020mmol) as a colorless glass. Mixture of diastereomers: ¹H NMR: (DMSO) [8.42 (d, J=6.8Hz), 7.15 (d, J=7.2Hz), 1H], 7.40-7.32 (m, 5H), [7.06 (d, J=8Hz), 7.05 (d, J=8Hz), 1H], 4.78-4.68 (m, 1H), [4.49 (s), 4.48 (s), 2H], 4.32-3.75 (m, 5H), 3.60-3.23 (m, 10H). MS: (M+H)⁺ 440.

10

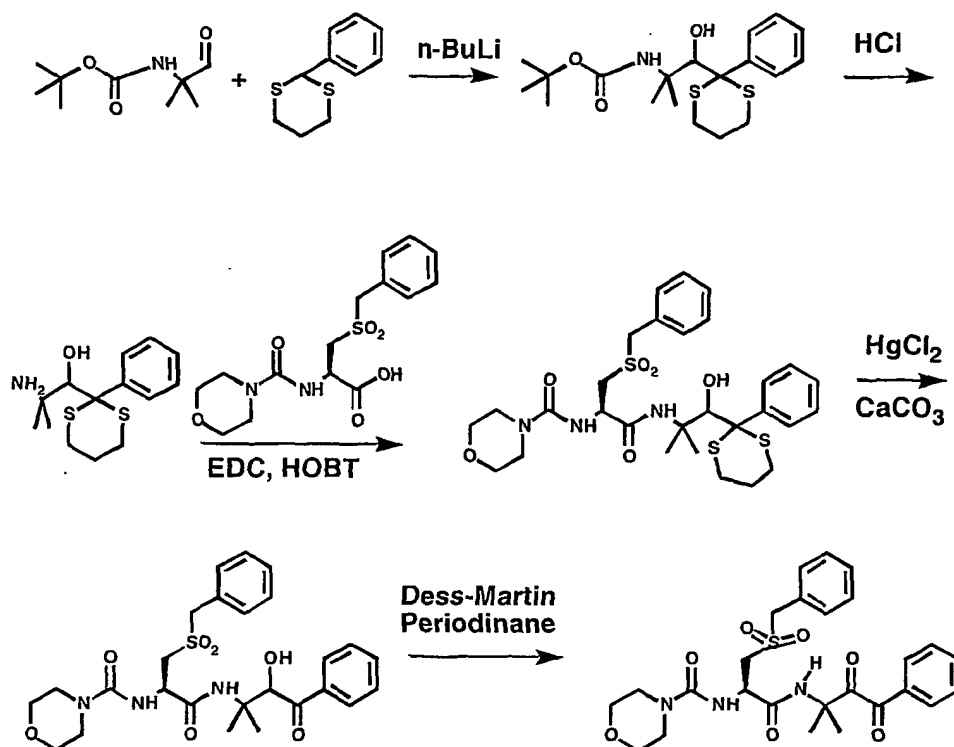
EXAMPLE 13

Morpholine-4-carboxylic acid [1-(2-hydroxy-1,1-dimethyl-3-oxo-3-phenyl-propylcarbamoyl)-2-phenylmethanesulfonyl-ethyl]-amide

(Compound 17)

15

-67-



- Step 1 To a flask fitted with a septum and stirbar under a nitrogen atmosphere containing 4.1 g (20 mmol) of 2-phenyl-1,3-dithiane (Aldrich) was added dry distilled THF (20 mL). The solution was cooled to $-30\text{ }^{\circ}\text{C}$ and *n*-butyl lithium (1.6M in
- 5 pentane, 16.8 mmol, 10.5 mL) was added slowly by syringe. The reaction mixture was warmed to $-20\text{ }^{\circ}\text{C}$ and held at that temperature for 30 minutes, and then held at $-10\text{ }^{\circ}\text{C}$ for 15 minutes. The yellow solution was cooled to $-78\text{ }^{\circ}\text{C}$ and (1,1-dimethyl-2-oxo-ethyl)-carbamic acid *tert*-butyl ester (1.5 g, 8 mmol, in 5 ml THF) was added rapidly (over 30 seconds) and 60 seconds later a solution of 2 mL acetic acid and 5 mL THF
- 10 was added rapidly. The cooling bath was removed and 4 minutes later water was added and the mixture was extracted with ethyl acetate. The solvent was removed under reduced pressure and then recrystallized from 10 ml of ethyl acetate. The white crystals were washed three times with ethyl acetate and dried under reduced pressure to

afford [2-hydroxy-1,1-dimethyl-2-(2-phenyl-[1,3]dithian-2-yl)-ethyl]-carbamic acid *tert*-butyl ester (1.6g, 52%).

Step 2 To [2-hydroxy-1,1-dimethyl-2-(2-phenyl-[1,3]dithian-2-yl)-ethyl]-carbamic acid *tert*-butyl ester (1 g, 2.6 mmol) in 4.8 mL dioxane at 10 °C was added hydrochloric acid (4.8 mL, 4M in dioxane). The solution was warmed to 23 °C. After 2 hours the solution was concentrated to 4 ml and diluted with ether to afford a white precipitate that was collected by filtration. The mother liquor was concentrated to a paste and triturated with ether. The solids were combined to afford 726 mg of 2-amino-2-methyl-1-(2-phenyl-[1,3]dithian-2-yl)-propan-1-ol (98% yield).

Step 3 2-Amino-2-methyl-1-(2-phenyl-[1,3]dithian-2-yl)-propan-1-ol and 2-[(morpholine-4-carbonyl)-amino]-3-phenylmethanesulfonyl-propionic acid were coupled using the standard peptide coupling conditions hereinbefore described to afford morpholine-4-carboxylic acid {1-[2-hydroxy-1,1-dimethyl-2-(2-phenyl-[1,3]dithian-2-yl)-ethylcarbamoyl]-2-phenylmethanesulfonyl-ethyl}-amide (270mg, 78%).

Step 4 To morpholine-4-carboxylic acid {1-[2-hydroxy-1,1-dimethyl-2-(2-phenyl-[1,3]dithian-2-yl)-ethylcarbamoyl]-2-phenylmethanesulfonyl-ethyl}-amide (200 mg, 0.32 mmol) in 5.25 ml of 4:1 acetonitrile:water at 23 °C was simultaneously added finely ground HgCl₂ (192 mg, 0.7 mmol) and finely ground calcium carbonate (80 mg, 0.8 mmol) with stirring. The mixture was stirred for 10 minutes and then diluted with ethyl acetate. Methylene chloride was added and the organics were washed with water. After separation the organic layer concentrated to a gum that solidified upon addition of

ether. The ether was removed under reduced pressure to afford a white solid. The solid was dissolved in a minimum of hot methylene chloride and filtered to remove insoluble material. The solution was concentrated to afford morpholine-4-carboxylic acid [1-(2-hydroxy-1,1-dimethyl-3-oxo-3-phenyl-propylcarbamoyl)-2-phenylmethanesulfonyl-ethyl]-amide (165mg, 100% yield).

Step 5 [1-(2-hydroxy-1,1-dimethyl-3-oxo-3-phenyl-propylcarbamoyl)-2-phenylmethanesulfonyl-ethyl]-amide was oxidized in the usual manner to afford morpholine-4-carboxylic acid [1-(2-hydroxy-1,1-dimethyl-3-oxo-3-phenyl-propylcarbamoyl)-2-phenylmethanesulfonyl-ethyl]-amide. ¹HNMR: (CDCl₃) [8.0 (d, J = 8 Hz) 1H], 7.7-7.2 (m, 10H), [5.9 (d, J = 6Hz) 1H], [4.8 (d, J = 6Hz) 1H], [4.3 (d, J = 14, Hz) 1H], [4.1 (d, J = 14 Hz) 1H], 3.7 (m, 4H), 3.36 (m, 4H), [3.3 (d, J = 2 Hz) 1H], [3.29 (d, J = 2 Hz) 1H], 1.7(s, 6H). LCMS: elution time = 3.71 min. 527.6(M-1), 529.6(M+1). (MS: API 150EX. LC: HP Agilent 1100 Series. Column: Phenomenex, 5u ODS3 100A 100X3mm.; Flow Rate: 2ml/min. Two solvent gradient: Solvent A, 99% water, 1% acetonitrile, 0.1% AcOH. Solvent B, 99% acetonitrile, 1% water, 0.1% AcOH. Gradient from 100% A, 0% B to 0% A, 100% B from t = 0 to t = 6min. Then gradient back to 100% A, 0% B from t = 7 to t = 15 min.).

By proceeding in a similar manner to Example 13 but using 3-(2-difluoromethoxy-phenylmethanesulfonyl)-2-[(morpholine-4-carbonyl)-amino]-propionic acid in step 3 there was prepared morpholine-4-carboxylic acid [2-(2-difluoromethoxy-phenylmethanesulfonyl)-1-(1,1-dimethyl-2,3-dioxo-3-phenyl-propylcarbamoyl)-ethyl]-amide. LC-MS: elution time = 3.95 min. 593.4(M-1),

596.2(M+1). (MS: API 150EX. LC: HP Agilent 1100 Series. Column: Phenomenex, 5u ODS3 100A 100X3mm.; Flow Rate: 2ml/min. Two solvent gradient: Solvent A, 99% water, 1% acetonitrile, 0.1% AcOH. Solvent B, 99% acetonitrile, 1% water, 0.1% AcOH. Gradient from 100% A, 0% B to 0% A, 100% B from t = 0 to t = 6min. Then
5 gradient back to 100% A, 0% B from t = 7 to t = 15 min.)

EXAMPLE 14

Cathepsin S Assay

10 Solutions of test compounds in varying concentrations were prepared in 10 μ L of dimethyl sulfoxide (DMSO) and then diluted into assay buffer (40 μ L, comprising: MES, 50 mM (pH 6.5); EDTA, 2.5 mM; and NaCl, 100 mM). Human cathepsin S (0.158 pMoles in 25 μ L of assay buffer) was added to the dilutions. The assay solutions were mixed for 5-10 seconds on a shaker plate, covered and incubated for 30 minutes at ambient
15 temperature. Z-Val-Val-Arg-AMC (9 nMoles in 25 μ L of assay buffer) was added to the assay solutions and hydrolysis was followed spectrophotometrically at (λ 460 nm) for 5 minutes. Apparent inhibition constants (K_i) were calculated from the enzyme progress curves using standard mathematical models.

20

EXAMPLE 15

Cathepsin B Assay

Solutions of test compounds in varying concentrations were prepared in 10 μ L of dimethyl sulfoxide (DMSO) and then diluted into assay buffer (40 μ L, comprising: *N,N*-bis(2-hydroxyethyl)-2-aminoethanesulfonic acid (BES), 50 mM (pH 6); polyoxyethylenesorbitan monolaurate, 0.05%; and dithiothreitol (DTT), 2.5 mM). Human cathepsin B (0.025 pMoles in 25 μ L of assay buffer) was added to the dilutions. The assay solutions were mixed for 5-10 seconds on a shaker plate, covered and incubated for 30 minutes at ambient temperature. Z-FR-AMC (20 nMoles in 25 μ L of assay buffer) was added to the assay solutions and hydrolysis was followed spectrophotometrically at (λ 460 nm) for 5 minutes. Apparent inhibition constants (K_i) were calculated from the enzyme progress curves using standard mathematical models.

EXAMPLE 16

Cathepsin K Assay

Solutions of test compounds in varying concentrations were prepared in 10 μ L of dimethyl sulfoxide (DMSO) and then diluted into assay buffer (40 μ L, comprising: MES, 50 mM (pH 5.5); EDTA, 2.5 mM; and DTT, 2.5 mM). Human cathepsin K (0.0906 pMoles in 25 μ L of assay buffer) was added to the dilutions. The assay solutions were mixed for 5-10 seconds on a shaker plate, covered and incubated for 30 minutes at ambient temperature. Z-Phe-Arg-AMC (4 nMoles in 25 μ L of assay buffer) was added to the assay solutions and hydrolysis was followed spectrophotometrically at (λ 460 nm) for 5 minutes. Apparent inhibition constants (K_i) were calculated from the enzyme progress curves using standard mathematical models.

EXAMPLE 17

Cathepsin L Assay

5 Solutions of test compounds in varying concentrations were prepared in 10 μ L of dimethyl sulfoxide (DMSO) and then diluted into assay buffer (40 μ L, comprising: MES, 50 mM (pH 5.5); EDTA, 2.5 mM; and DTT, 2.5 mM). Human cathepsin L (0.05 pMoles in 25 μ L of assay buffer) was added to the dilutions. The assay solutions were mixed for 5-10 seconds on a shaker plate, covered and incubated for 30 minutes at ambient
10 temperature. Z-Phe-Arg-AMC (1 nMoles in 25 μ L of assay buffer) was added to the assay solutions and hydrolysis was followed spectrophotometrically at (λ 460 nm) for 5 minutes. Apparent inhibition constants (K_i) were calculated from the enzyme progress curves using standard mathematical models.

 Some of the compounds of the invention tested according to the above-described
15 assays for protease inhibition were observed to exhibit selective cathepsin S inhibitory activity. The apparent inhibition constants (K_i) for compounds of the invention, against Cathepsin S, were in the range from about 10^{-10} M to about 10^{-7} M.

EXAMPLE 18

20 Representative Pharmaceutical Formulations Containing a Compound of Formula I

ORAL FORMULATION

-73-

	Compound of Formula I	10-100 mg
	Citric Acid Monohydrate	105 mg
	Sodium Hydroxide	18 mg
	Flavoring	
5	Water	q.s. to 100 mL

INTRAVENOUS FORMULATION

	Compound of Formula I	0.1-10 mg
	Dextrose Monohydrate	q.s. to make isotonic
10	Citric Acid Monohydrate	1.05 mg
	Sodium Hydroxide	0.18 mg
	Water for Injection	q.s. to 1.0 mL

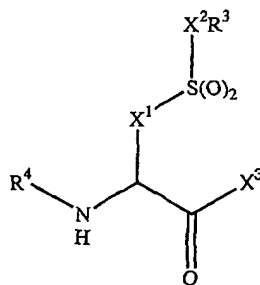
TABLET FORMULATION

15	Compound of Formula I	1%
	Microcrystalline Cellulose	73%
	Stearic Acid	25%
	Colloidal Silica	1%.

20

WE CLAIM:

1. A compound of Formula I:



I

in which:

X^1 and X^2 are both methylene or X^1 is ethylene and X^2 is a bond;

- 10 R^3 is $-\text{CR}^5=\text{CHR}^6$, $-\text{CR}^5(\text{CR}^6_3)_2$ or $-\text{CR}^7=\text{NR}^8$, wherein R^5 is hydrogen and R^6 is hydrogen or (C_{1-4}) alkyl or R^5 and R^6 together with the atoms to which R^5 and R^6 are attached form (C_{3-12}) cycloalkenyl, hetero (C_{5-12}) cycloalkenyl, (C_{6-12}) aryl, hetero (C_{6-12}) aryl, (C_{9-12}) bicycloaryl or hetero (C_{8-12}) bicycloaryl and R^7 and R^8 together with the atoms to which R^7 and R^8 are attached form hetero (C_{5-12}) cycloalkenyl, hetero (C_{6-12}) aryl or
- 15 hetero (C_{8-12}) bicycloaryl, wherein R^3 optionally is substituted by 1 to 5 radicals independently selected from a group consisting of (C_{1-4}) alkyl, cyano, halo, halo-substituted (C_{1-4}) alkyl, nitro, $-\text{X}^4\text{NR}^9\text{R}^9$, $-\text{X}^4\text{OR}^9$, $-\text{X}^4\text{SR}^9$, $-\text{X}^4\text{C}(\text{O})\text{NR}^9\text{R}^9$, $-\text{X}^4\text{C}(\text{O})\text{OR}^9$, $-\text{X}^4\text{S}(\text{O})\text{R}^{10}$, $-\text{X}^4\text{S}(\text{O})_2\text{R}^{10}$ and $-\text{X}^4\text{C}(\text{O})\text{R}^{10}$, wherein X^4 is a bond or (C_{1-2}) alkylene, R^9 at each occurrence independently is hydrogen, (C_{1-3}) alkyl or halo-substituted (C_{1-3}) alkyl and
- 20 R^{10} is (C_{1-3}) alkyl or halo-substituted (C_{1-3}) alkyl; and

R^4 is $-C(O)X^5R^{11}$ or $-S(O)_2X^5R^{11}$, wherein X^5 is a bond, $-O-$ or $-NR^{12}-$, wherein R^{12} is hydrogen or (C_{1-6}) alkyl, and R^{11} is (i) (C_{1-6}) alkyl optionally substituted by $-OR^{13}$, $-SR^{13}$, $-S(O)R^{13}$, $-S(O)_2R^{13}$, $-C(O)R^{13}$, $-C(O)OR^{13}$, $-C(O)NR^{13}R^{14}$, $-NR^{13}R^{14}$, $-NR^{14}C(O)R^{13}$, $-NR^{14}C(O)OR^{13}$, $-NR^{14}C(O)NR^{13}R^{14}$ or $-NR^{14}C(NR^{14})NR^{13}R^{14}$, wherein

5 R^{13} is (C_{3-12}) cycloalkyl (C_{0-3}) alkyl, hetero (C_{5-12}) cycloalkyl (C_{0-3}) alkyl, (C_{6-12}) aryl (C_{0-3}) alkyl, hetero (C_{5-12}) aryl (C_{0-3}) alkyl, (C_{9-12}) bicycloaryl (C_{0-3}) alkyl or hetero (C_{8-12}) bicycloaryl (C_{0-3}) alkyl and R^{14} at each occurrence independently is hydrogen or (C_{1-6}) alkyl, or (ii) (C_{3-12}) cycloalkyl (C_{0-3}) alkyl, hetero (C_{5-12}) cycloalkyl (C_{0-3}) alkyl, (C_{6-12}) aryl (C_{0-3}) alkyl, hetero (C_{5-12}) aryl (C_{0-3}) alkyl, (C_{9-12}) bicycloaryl (C_{0-3}) alkyl or

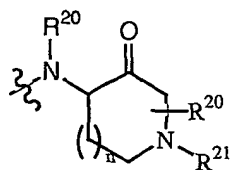
10 hetero (C_{8-12}) bicycloaryl (C_{0-3}) alkyl or (iii) (C_{3-6}) cycloalkyl (C_{0-3}) alkyl, hetero (C_{5-6}) cycloalkyl (C_{0-3}) alkyl, phenyl (C_{0-3}) alkyl or hetero (C_{5-6}) aryl (C_{0-3}) alkyl substituted by $-X^6OR^{15}$, $-X^6SR^{15}$, $-X^6S(O)R^{15}$, $-X^6S(O)_2R^{15}$, $-X^6C(O)R^{15}$, $-X^6C(O)OR^{15}$, $-X^6C(O)NR^{15}R^{16}$, $-X^6NR^{15}R^{16}$, $-X^6NR^{16}C(O)R^{15}$, $-X^6NR^{16}C(O)OR^{15}$, $-X^6NR^{16}C(O)NR^{15}R^{16}$, $-X^6NR^{16}C(O)OR^{16}$, $-X^6NR^{16}C(NR^{16})NR^{15}R^{16}$, wherein X^6 is a

15 bond or methylene, R^{15} is (C_{3-6}) cycloalkyl (C_{0-3}) alkyl, hetero (C_{5-6}) cycloalkyl (C_{0-3}) alkyl, phenyl (C_{0-3}) alkyl or hetero (C_{5-6}) aryl (C_{0-3}) alkyl and R^{16} is hydrogen or (C_{1-6}) alkyl; wherein R^4 optionally further contains 1 to 5 substituents which when occurring within an alicyclic or aromatic ring system are radicals independently selected from a group consisting of (C_{1-6}) alkyl, (C_{1-6}) alkylidene, cyano, halo, nitro, halo-substituted (C_{1-3}) alkyl, $-X^6NR^{17}R^{17}$,

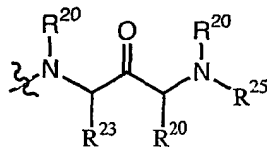
20 $-X^6NR^{17}C(O)OR^{17}$, $-X^6NR^{17}C(O)NR^{17}R^{17}$, $-X^6NR^{17}C(NR^{17})NR^{17}R^{17}$, $-X^6OR^{17}$, $-X^6SR^{17}$, $-X^6C(O)OR^{17}$, $-X^6C(O)NR^{17}R^{17}$, $-X^6S(O)_2NR^{17}R^{17}$, $-X^6P(O)(OR^{18})OR^{17}$, $-X^6OP(O)(OR^{18})OR^{17}$, $-X^6NR^{17}C(O)R^{18}$, $-X^6S(O)R^{18}$, $-X^6S(O)_2R^{18}$ and $-X^6C(O)R^{18}$ and when occurring within an aliphatic moiety are radicals independently selected from a group

consisting of cyano, halo, nitro, $-\text{NR}^{17}\text{R}^{17}$, $-\text{NR}^{17}\text{C}(\text{O})\text{OR}^{17}$, $-\text{NR}^{17}\text{C}(\text{O})\text{NR}^{17}\text{R}^{17}$,
 $-\text{NR}^{17}\text{C}(\text{NR}^{17})\text{NR}^{17}\text{R}^{17}$, $-\text{OR}^{17}$, $-\text{SR}^{17}$, $-\text{C}(\text{O})\text{OR}^{17}$, $-\text{C}(\text{O})\text{NR}^{17}\text{R}^{17}$, $-\text{S}(\text{O})_2\text{NR}^{17}\text{R}^{17}$,
 $-\text{P}(\text{O})(\text{OR}^{17})\text{OR}^{17}$, $-\text{OP}(\text{O})(\text{OR}^{17})\text{OR}^{17}$, $-\text{NR}^{17}\text{C}(\text{O})\text{R}^{18}$, $-\text{S}(\text{O})\text{R}^{18}$, $-\text{S}(\text{O})_2\text{R}^{18}$ and
 $-\text{C}(\text{O})\text{R}^{18}$, wherein X^6 is a bond or (C_{1-6}) alkylene, R^{17} at each occurrence independently
 5 is hydrogen, (C_{1-6}) alkyl or halo-substituted (C_{1-3}) alkyl and R^{18} is (C_{1-6}) alkyl or
 halo-substituted (C_{1-3}) alkyl;

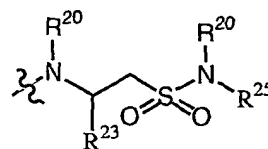
X^3 is a group of Formula (a), (b) or (c):



(a)



(b)



(c)

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n is 0, 1 or 2;

R^{20} is selected from the group consisting of hydrogen, (C_{1-6}) alkyl,
 (C_{3-12}) cycloalkyl (C_{0-6}) alkyl, hetero (C_{5-12}) cycloalkyl (C_{0-6}) alkyl, (C_{6-12}) aryl (C_{0-6}) alkyl and
 hetero (C_{5-12}) aryl (C_{0-6}) alkyl;

15 R^{21} is selected from the group consisting of hydrogen, (C_{1-9}) alkyl,
 (C_{3-12}) cycloalkyl (C_{0-6}) alkyl, hetero (C_{5-12}) cycloalkyl (C_{0-6}) alkyl, (C_{6-12}) aryl (C_{0-6}) alkyl,
 hetero (C_{5-12}) aryl (C_{0-6}) alkyl, (C_{9-12}) bicycloaryl (C_{0-3}) alkyl, hetero (C_{8-12}) -
 bicycloaryl (C_{0-3}) alkyl, $-\text{C}(\text{O})\text{R}^{26}$, $-\text{C}(\text{S})\text{R}^{26}$, $-\text{S}(\text{O})_2\text{R}^{26}$, $-\text{C}(\text{O})\text{OR}^{26}$, $-\text{C}(\text{O})\text{N}(\text{R}^{26})\text{R}^{27}$,
 $-\text{C}(\text{S})\text{N}(\text{R}^{26})\text{R}^{27}$ and $-\text{S}(\text{O})_2\text{N}(\text{R}^{27})\text{R}^{26}$;

20 R^{23} is selected from (C_{1-6}) alkyl, (C_{4-6}) alkenyl, (C_{3-12}) cycloalkyl (C_{0-6}) alkyl,
 hetero (C_{5-12}) cycloalkyl (C_{0-6}) alkyl, (C_{6-12}) aryl (C_{0-6}) alkyl or hetero (C_{5-12}) aryl (C_{0-6}) alkyl

optionally substituted with amino, -NHC(O)R^{15} or -R^{15} wherein R^{15} is as described above;

R^{25} is selected from hydrogen, $(\text{C}_{1-6})\text{alkyl}$, $(\text{C}_{3-12})\text{cycloalkyl}(\text{C}_{0-6})\text{alkyl}$, hetero $(\text{C}_{5-12})\text{cycloalkyl}(\text{C}_{0-6})\text{alkyl}$, $(\text{C}_{6-12})\text{aryl}(\text{C}_{0-6})\text{alkyl}$, hetero $(\text{C}_{5-13})\text{aryl}(\text{C}_{0-6})\text{alkyl}$, $\text{-X}^4\text{NHR}^{15}$, $\text{-X}^4\text{S(O)}_2\text{R}^{26}$ or $\text{-X}^4\text{C(O)R}^{17}\text{NR}^{17}\text{C(O)R}^{17}$ wherein R^{15} , R^{17} and X^4 are as

5 described above;

R^{26} is selected from the group consisting of hydrogen, $(\text{C}_{1-6})\text{alkyl}$, $(\text{C}_{3-12})\text{cycloalkyl}(\text{C}_{0-6})\text{alkyl}$, hetero $(\text{C}_{5-12})\text{cycloalkyl}(\text{C}_{0-6})\text{alkyl}$, $(\text{C}_{6-12})\text{aryl}(\text{C}_{0-6})\text{alkyl}$, hetero $(\text{C}_{5-12})\text{aryl}(\text{C}_{0-6})\text{alkyl}$, $(\text{C}_{9-12})\text{bicycloaryl}(\text{C}_{0-3})\text{alkyl}$ or hetero $(\text{C}_{8-12})\text{-bicycloaryl}(\text{C}_{0-3})\text{alkyl}$;

10 R^{27} is hydrogen, $(\text{C}_{1-6})\text{alkyl}$, $(\text{C}_{3-12})\text{cycloalkyl}(\text{C}_{0-6})\text{alkyl}$, hetero $(\text{C}_{5-12})\text{cycloalkyl}(\text{C}_{0-6})\text{alkyl}$, $(\text{C}_{6-12})\text{aryl}(\text{C}_{0-6})\text{alkyl}$ or hetero $(\text{C}_{5-12})\text{aryl}(\text{C}_{0-6})\text{alkyl}$;

wherein X^3 optionally further contains 1 to 5 substituents which when occurring

within an alicyclic or aromatic ring system are radicals independently selected from a group consisting of $(\text{C}_{1-6})\text{alkyl}$, $(\text{C}_{1-6})\text{alkylidene}$, cyano, halo, nitro, halo-substituted

15 $(\text{C}_{1-3})\text{alkyl}$, $\text{-X}^6\text{NR}^{17}\text{R}^{17}$, $\text{-X}^6\text{NR}^{17}\text{C(O)OR}^{17}$, $\text{-X}^6\text{NR}^{17}\text{C(O)NR}^{17}\text{R}^{17}$, $\text{-X}^6\text{NR}^{17}\text{C(NR}^{17})\text{NR}^{17}\text{R}^{17}$, $\text{-X}^6\text{OR}^{17}$, $\text{-X}^6\text{C(O)R}^{17}$, $\text{-X}^6\text{OR}^{15}$, $\text{-X}^6\text{SR}^{17}$, $\text{-X}^6\text{C(O)OR}^{17}$, $\text{-X}^6\text{C(O)NR}^{17}\text{R}^{17}$, $\text{-X}^6\text{S(O)}_2\text{NR}^{17}\text{R}^{17}$, $\text{-X}^6\text{P(O)(OR}^8\text{)OR}^{17}$, $\text{-X}^6\text{OP(O)(OR}^8\text{)OR}^{17}$, $\text{-X}^6\text{NR}^{17}\text{C(O)R}^{18}$, $\text{-X}^6\text{S(O)R}^{18}$, $\text{-X}^6\text{S(O)}_2\text{R}^{18}$ and $\text{-X}^6\text{C(O)R}^{18}$ and when occurring within

an aliphatic moiety are radicals independently selected from a group consisting of cyano,

20 halo, nitro, $\text{-NR}^{17}\text{R}^{17}$, $\text{-NR}^{17}\text{C(O)OR}^{17}$, $\text{-NR}^{17}\text{C(O)NR}^{17}\text{R}^{17}$, $\text{-NR}^{17}\text{C(NR}^{17})\text{NR}^{17}\text{R}^{17}$, -OR^{17} , -SR^{17} , -C(O)OR^{17} , $\text{-C(O)NR}^{17}\text{R}^{17}$, $\text{-S(O)}_2\text{NR}^{17}\text{R}^{17}$, $\text{-P(O)(OR}^{17}\text{)OR}^{17}$, $\text{-OP(O)(OR}^{17}\text{)OR}^{17}$, $\text{-NR}^{17}\text{C(O)R}^{18}$, -S(O)R^{18} , $\text{-S(O)}_2\text{R}^{18}$ and -C(O)R^{18} , wherein R^{15} , R^{17} , R^{18} and X^6 are as described above; and the *N*-oxide derivatives, prodrug derivatives,

protected derivatives, individual isomers and mixtures of isomers thereof; and the

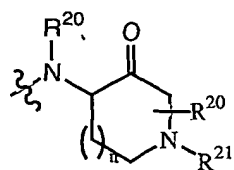
pharmaceutically acceptable salts and solvates of such compounds and the N-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof.

5 2. The compound of claim 1 in which X^1 and X^2 are both methylene or X^1 is ethylene and X^2 is a bond; R^3 is $-CR^5=CHR^6$, $-CR^5(CR^6_3)_2$ or $-CR^7=NR^8$, wherein R^5 is hydrogen and R^6 is hydrogen or (C_{1-4}) alkyl or R^5 and R^6 together with the atoms to which R^5 and R^6 are attached form (C_{3-12}) cycloalkenyl, (C_{6-12}) aryl, hetero (C_{6-12}) aryl or (C_{9-12}) bicycloaryl and R^7 and R^8 together with the atoms to which R^7 and R^8 are attached form
10 hetero (C_{5-12}) cycloalkenyl or hetero (C_{6-12}) aryl, wherein R^3 optionally is substituted by 1 to 5 radicals independently selected from a group consisting of (C_{1-4}) alkyl, cyano, halo, halo-substituted (C_{1-4}) alkyl, $-X^4OR^9$ and $-X^4C(O)OR^9$, wherein X^4 is a bond or (C_{1-2}) alkylene, R^9 at each occurrence independently is (C_{1-3}) alkyl or halo-substituted (C_{1-3}) alkyl; and the N-oxide derivatives, prodrug derivatives, protected derivatives,
15 individual isomers and mixtures of isomers thereof; and the pharmaceutically acceptable salts and solvates of such compounds and the N-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof.

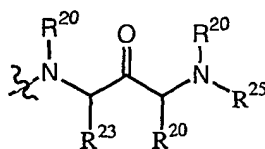
3. The compound of claim 2 in which R^4 is $-C(O)X^5R^{11}$ or $-S(O)_2X^5R^{11}$, wherein X^5
20 is a bond, $-O-$ or $-NR^{12}-$, wherein R^{12} is hydrogen or (C_{1-6}) alkyl, and R^{11} is (i) (C_{1-6}) alkyl or (ii) hetero (C_{5-12}) cycloalkyl (C_{0-3}) alkyl, (C_{6-12}) aryl (C_{0-3}) alkyl, hetero (C_{5-12}) aryl (C_{0-3}) alkyl, (C_{9-12}) bicycloaryl (C_{0-3}) alkyl or hetero (C_{8-12}) bicycloaryl (C_{0-3}) alkyl or (iii) hetero (C_{5-6}) cycloalkyl (C_{0-3}) alkyl or phenyl (C_{0-3}) alkyl substituted by $-X^6OR^{15}$, $-X^6C(O)R^{15}$ or $-X^6NR^{16}C(O)OR^{16}$, wherein X^6 is a bond or methylene, R^{15} is phenyl (C_{0-3}) alkyl or

hetero(C₅₋₆)aryl(C₀₋₃)alkyl and R¹⁶ is hydrogen or (C₁₋₆)alkyl; wherein R⁴ optionally further contains 1 to 5 substituents which when occurring within an alicyclic or aromatic ring system are radicals independently selected from a group consisting of (C₁₋₆)alkyl, halo, -X⁶NR¹⁷R¹⁷, -X⁶OR¹⁷, -X⁶C(O)OR¹⁷, -X⁶NC(O)R¹⁶ and -X⁶C(O)R¹⁸, R¹⁷ at each
 5 occurrence independently is hydrogen, (C₁₋₆)alkyl or halo-substituted (C₁₋₃)alkyl and R¹⁸ is (C₁₋₆)alkyl or halo-substituted (C₁₋₃)alkyl; and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof; and the pharmaceutically acceptable salts and solvates of such compounds and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of
 10 isomers thereof.

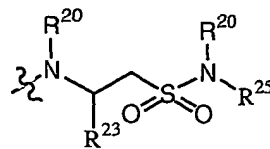
4. The compound of claim 3 in which X³ is a group of Formula (a), (b) or (c):



(a)



(b)



(c)

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n is 0, 1 or 2;

R²⁰ is selected from the group consisting of hydrogen and (C₁₋₆)alkyl;

R²¹ is selected from the group consisting of (C₁₋₉)alkyl, (C₆₋₁₂)aryl(C₀₋₆)alkyl, -C(O)R²⁶, -S(O)₂R²⁶, -C(O)OR²⁶ and -C(O)N(R²⁶)R²⁷;

20 R²³ is selected from (C₁₋₆)alkyl optionally substituted with amino, -NHC(O)R¹⁵ or -R¹⁵ wherein R¹⁵ is as described above;

R^{25} is selected from (C_{1-6}) alkyl, (C_{6-12}) aryl (C_{0-6}) alkyl, $-X^4S(O)_2R^{26}$ or $-X^4C(O)R^{17}NR^{17}C(O)R^{17}$ wherein R^{17} and X^4 are as described above and R^{26} is as described below;

R^{26} is selected from the group consisting of (C_{1-6}) alkyl, hetero (C_{5-12}) cycloalkyl (C_{0-6}) alkyl, (C_{6-12}) aryl (C_{0-6}) alkyl, hetero (C_{5-12}) aryl (C_{0-6}) alkyl and (C_{9-12}) bicycloaryl (C_{0-3}) alkyl;

R^{27} is (C_{1-6}) alkyl;

wherein X^3 optionally further contains 1 to 5 substituents which when occurring within an alicyclic or aromatic ring system are radicals independently selected from a group consisting of (C_{1-6}) alkyl, cyano, halo, $-X^6OR^{17}$, $-X^6C(O)R^{17}$ and $-X^6OR^{15}$; and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof; and the pharmaceutically acceptable salts and solvates of such compounds and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof.

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5. The compound of claim 4 in which R^3 is selected from the group consisting of phenyl, pyridin-2-yl, pyridin-3-yl, pyridin-4-yl, vinyl, 2-difluoromethoxyphenyl, 1-oxy-pyridin-2-yl, 4-methoxyphenyl, 4-methylphenyl, 2-methylphenyl, 4-chlorophenyl, 3,5-dimethylphenyl, 4-trifluoromethylphenyl, 4-trifluoromethoxyphenyl, 2-bromophenyl, naphthalen-2-yl, 3,4-dichlorophenyl, 3-methylphenyl, 3-trifluoromethylphenyl, 3-trifluoromethoxyphenyl, 2,3,4,5,6-pentafluoro-phenyl, 2-fluorophenyl, 2-chlorophenyl, 2-cyano-phenyl, 2-trifluoromethylphenyl, 4-*tert*-butyl-phenyl, 3-chlorophenyl, 4-bromophenyl, 2-fluoro-3-chloro-phenyl, 2-fluoro-3-methyl-phenyl, 3-fluorophenyl, 2,5-difluorophenyl, 3-bromophenyl, 2,5-dichlorophenyl, 2,6-difluorophenyl, 3-cyano-phenyl,

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4-cyano-phenyl, 2-trifluoromethoxyphenyl, 2,3-difluorophenyl, biphenyl, 2-bromo-5-fluoro-phenyl, 4-fluorophenyl, 3,4-difluorophenyl, 2,4-difluorophenyl, 2,4,6-trifluorophenyl, 2,4,5-trifluorophenyl, 2,3,4-trifluorophenyl, 2-chloro-5-trifluoromethylphenyl, 2,4-bis-trifluoromethylphenyl, 2,5,6-trifluorophenyl, 2-fluoro-3-trifluoromethylphenyl, 2-fluoro-4-trifluoromethylphenyl, 2-fluoro-5-trifluoromethylphenyl, 2,3,5-trifluorophenyl, 2-fluoro-5-trifluoromethylphenyl, 5-fluoro-2-trifluoromethylphenyl, 4-fluoro-3-trifluoromethylphenyl, 2-methoxyphenyl, 3,5-bis-trifluoromethylphenyl, 4-difluoromethoxyphenyl, 3-difluoromethoxyphenyl, 2,6-dichlorophenyl, 4-carboxyphenyl, cyclohexyl, cyclopropyl, isopropyl, thiophen-2-yl, 5-chloro-thiophen-2-yl and 3,5-dimethyl-isoxazol-4-yl.

6. The compound of claim 5 in which R⁴ is benzoyl, morpholine-4-carbonyl, acetyl, furan-3-carbonyl, 2-methoxy-benzoyl, 3-methoxy-benzoyl, naphthalene-2-carbonyl, benzo[1,3]dioxole-5-carbonyl, 3-pyridin-3-yl-acryloyl, benzofuran-2-carbonyl, furan-2-carbonyl, *tert*-butoxy-carbonyl, biphenyl-4-carbonyl, quinoline-2-carbonyl, quinoline-3-carbonyl, 3-acetyl-benzoyl, 4-phenoxy-benzoyl, 3-hydroxy-benzoyl, 4-hydroxy-benzoyl, pyridine-3-carbonyl, 3-(*tert*-butoxycarbonylamino-methyl)-benzoyl, 4-carbonyl-piperazine-1-carboxylic acid *tert*-butyl ester, 4-carbonyl-piperazine-1-carboxylic acid ethyl ester, 4-(furan-2-carbonyl)-piperazine-1-carbonyl, pyridine-4-carbonyl, 1-oxy-pyridine-4-carbonyl, 1-oxy-pyridine-3-carbonyl, thiophene-2-carbonyl, thiophene-3-carbonyl, 4-benzoyl-benzoyl, 5-methyl-thiophene-2-carbonyl, 3-chloro-thiophene-2-carbonyl, 3-bromo-thiophene-2-carbonyl, 4-chloro-benzoyl, 3-flouro-4-methoxy-benzoyl, 4-methoxy-benzoyl, 4-triflouromethoxy-benzoyl, 3,4-diflouro-benzoyl, 4-fluoro-benzoyl, 3,4-dimethoxy-benzoyl, 3-methyl-benzoyl, 4-bromo-benzoyl, 4-triflouromethyl-benzoyl, 3-benzoyl-

benzoyl, cyclopentane-carbonyl, benzo[b]thiophene-2-carbonyl, 3-chloro-benzo[b]thiophene-2-carbonyl, benzenesulfonyl, naphthalene-2-sulfonyl, 5-methyl-thiophene-2-sulfonyl, thiophene-2-sulfonyl, formamyl-methyl ester, 4-methyl-pentanoyl, formamyl-isobutyl ester, formamyl-monoallyl ester, formamyl-isopropyl ester, *N,N*-
 5 dimethyl-formamyl, *N*-isopropyl-formamyl, *N*-pyridin-4-yl-formamyl, *N*-pyridin-3-yl-formamyl, 3-phenyl-acryloyl, 1H-indole-5-carbonyl, pyridine-2-carbonyl, pyrazine-2-carbonyl, 3-hydroxy-pyridine-2-carbonyl, 2-amino-pyridine-3-carbonyl, 2-hydroxy-pyridine-3-carbonyl, 6-amino-pyridine-3-carbonyl, 6-hydroxy-pyridine-3-carbonyl, pyridazine-4-carbonyl, 3-phenoxy-benzoyl and 1-oxo-1,3-dihydro-isoindole-2-carbonyl.

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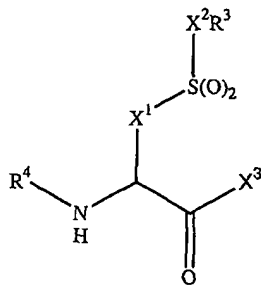
7. The compound of claim 6 in which X³ is selected from a group consisting of 4-amino-3-oxo-azepane-1-carboxylic acid benzyl ester, 4-amino-3-oxo-azepane-1-carboxylic acid isobutyl ester, 4-amino-1-benzoyl-azepan-3-one, 4-amino-1-benzenesulfonyl-azepan-3-one, 4-amino-1-(pyridine-2-sulfonyl)-azepan-3-one, 4-amino-1-(1-oxy-pyridine-2-sulfonyl)-azepan-3-one, 4-amino-1-(3,4-dichloro-benzenesulfonyl)-azepan-3-one, 4-amino-1-(2-flouro-benzenesulfonyl)-azepan-3-one, 4-amino-1-(3,4-dimethoxy-benzenesulfonyl)-azepan-3-one, 4-amino-1-(2-cyano-benzenesulfonyl)-azepan-3-one, 4-amino-1-(naphthalene-1-sulfonyl)-azepan-3-one, 4-amino-1-(thiophene-2-sulfonyl)-azepan-3-one, 4-amino-1-(thiazole-2-sulfonyl)-azepan-3-one, 4-amino-1-(pyrrolidine-1-sulfonyl)-azepan-3-one, 4-amino-1-methanesulfonyl-azepan-3-one, 4-amino-1-(pyrrolidine-1-carbonyl)-azepan-3-one, 4-amino-3-oxo-azepane-1-carboxylic-acid-dimethylamide, 4-amino-3-oxo-azepane-1-carboxylic-acid-benzylamide, 4-amino-1-benzyl-azepan-3-one, 4-amino-1-benzyl-piperidin-3-one, 4-amino-1-benzoyl-piperidin-3-one, 4-amino-1-benzoyl-pyrrolidin-3-one, 4-amino-1-benzyl-pyrrolidin-3-one, 4-amino-1-benzenesulfonyl-

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pyrrolidin-3-one, 4-amino-1-(5-methyl-hexyl)-pyrrolidin-3-one, 1-ethyl-2-oxo-3-(toluene-4-sulfonylamino)-butylamino, 1-ethyl-2-oxo-3-(4-phenoxy-benzenesulfonylamino)-propylamino, 1-ethyl-2-oxo-3-[4-(pyridin-3-yloxy)-benzenesulfonylamino]-propylamino, 3-(dibenzofuran-2-sulfonylamino)-1-ethyl-2-oxo-butylamino, 1-ethyl-3-[4-methyl-2-(4-methyl-pentanoylamino)-pentanoylamino]-2-oxo-propylamino, 5-amino-1-[(4-methoxy-phenylsulfamoyl)-methyl]-pentylamino, 5-benzyloxycarbonylamino-1-[(4-methoxy-phenylsulfamoyl)-methyl]-pentylamino, 1-[(4-methoxy-phenylsulfamoyl)-methyl]-3-phenyl-propylamino, 1-{[4-(1-hydroxy-ethyl)-phenylsulfamoyl]-methyl}-3-phenyl-propylamino, 1-[(4-acetyl-phenylsulfamoyl)-methyl]-3-phenyl-propylamino, 1-[(4-hydroxy-phenylsulfamoyl)-methyl]-3-phenyl-propylamino and 3-phenyl-1-[(2-phenylamino-ethylsulfamoyl)-methyl]-propylamino.

8. The compound of claim 7 selected from the group consisting of morpholine-4-carboxylic acid (1-{5-amino-1-[(4-methoxy-phenylsulfamoyl)-methyl]-pentylcarbamoyl}-2-phenylmethanesulfonyl-ethyl)-amide, (6-(4-methoxy-phenylsulfamoyl)-5-{2-[(morpholine-4-carbonyl)-amino]-3-phenylmethane-sulfonyl-propionylamino}-hexyl)-carbamic acid benzyl ester, morpholine-4-carboxylic acid (1-{1-[(4-methoxy-phenylsulfamoyl)-methyl]-3-phenyl-propylcarbamoyl}-2-phenylmethanesulfonyl-ethyl)-amide, morpholine-4-carboxylic acid [1-(3-benzenesulfonylamino-2-oxo-propylcarbamoyl)-2-phenylmethanesulfonyl-ethyl]-amide, morpholine-4-carboxylic acid [1-(1-benzoyl-4-oxo-pyrrolidin-3-ylcarbamoyl)-2-phenylmethanesulfonyl-ethyl]-amide, morpholine-4-carboxylic acid [1-(1-benzenesulfonyl-4-oxo-pyrrolidin-3-ylcarbamoyl)-2-phenylmethanesulfonyl-ethyl]-amide and 4-{2-[(Morpholine-4-carbonyl)-amino]-3-phenylmethanesulfonyl-propionylamino}-3-oxo-azepane-1-carboxylic acid benzyl ester.

9. A pharmaceutical composition comprising a therapeutically effective amount of a compound of Claim 1 in combination with a pharmaceutically acceptable excipient.
- 5 10. A method for treating a disease in an animal in which inhibition of Cathepsin S can prevent, inhibit or ameliorate the pathology and/or symptomology of the disease, which method comprises administering to the animal a therapeutically effective amount of compound of Claim 1 or a *N*-oxide derivative or individual isomer or mixture of isomers thereof; or a pharmaceutically acceptable salt or solvate of such compounds and the
- 10 *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof.
11. The use of a compound of Claim 1 in the manufacture of a medicament for treating a disease in an animal in which Cathepsin S activity contributes to the pathology and/or
- 15 symptomology of the disease.
12. A process for preparing a compound of Formula I:



I

in which:

X^1 and X^2 are both methylene or X^1 is ethylene and X^2 is a bond;

R^3 is $-CR^5=CHR^6$, $-CR^5(CR^6)_2$ or $-CR^7=NR^8$, wherein R^5 is hydrogen and R^6 is
 5 hydrogen or (C_{1-4}) alkyl or R^5 and R^6 together with the atoms to which R^5 and R^6 are
 attached form (C_{3-12}) cycloalkenyl, hetero (C_{5-12}) cycloalkenyl, (C_{6-12}) aryl, hetero (C_{6-12}) aryl,
 (C_{9-12}) bicycloaryl or hetero (C_{8-12}) bicycloaryl and R^7 and R^8 together with the atoms to
 which R^7 and R^8 are attached form hetero (C_{5-12}) cycloalkenyl, hetero (C_{6-12}) aryl or
 hetero (C_{8-12}) bicycloaryl, wherein R^3 optionally is substituted by 1 to 5 radicals
 10 independently selected from a group consisting of (C_{1-4}) alkyl, cyano, halo, halo-substituted
 (C_{1-4}) alkyl, nitro, $-X^4NR^9R^9$, $-X^4OR^9$, $-X^4SR^9$, $-X^4C(O)NR^9R^9$, $-X^4C(O)OR^9$,
 $-X^4S(O)R^{10}$, $-X^4S(O)_2R^{10}$ and $-X^4C(O)R^{10}$, wherein X^4 is a bond or (C_{1-2}) alkylene, R^9 at
 each occurrence independently is hydrogen, (C_{1-3}) alkyl or halo-substituted (C_{1-3}) alkyl and
 R^{10} is (C_{1-3}) alkyl or halo-substituted (C_{1-3}) alkyl; and

15 R^4 is $-C(O)X^5R^{11}$ or $-S(O)_2X^5R^{11}$, wherein X^5 is a bond, $-O-$ or $-NR^{12}-$, wherein
 R^{12} is hydrogen or (C_{1-6}) alkyl, and R^{11} is (i) (C_{1-6}) alkyl optionally substituted by $-OR^{13}$,
 $-SR^{13}$, $-S(O)R^{13}$, $-S(O)_2R^{13}$, $-C(O)R^{13}$, $-C(O)OR^{13}$, $-C(O)NR^{13}R^{14}$, $-NR^{13}R^{14}$,
 $-NR^{14}C(O)R^{13}$, $-NR^{14}C(O)OR^{13}$, $-NR^{14}C(O)NR^{13}R^{14}$ or $-NR^{14}C(NR^{14})NR^{13}R^{14}$, wherein
 R^{13} is (C_{3-12}) cycloalkyl (C_{0-3}) alkyl, hetero (C_{5-12}) cycloalkyl (C_{0-3}) alkyl, (C_{6-12}) aryl (C_{0-3}) alkyl,
 20 hetero (C_{5-12}) aryl (C_{0-3}) alkyl, (C_{9-12}) bicycloaryl (C_{0-3}) alkyl or
 hetero (C_{8-12}) bicycloaryl (C_{0-3}) alkyl and R^{14} at each occurrence independently is hydrogen
 or (C_{1-6}) alkyl, or (ii) (C_{3-12}) cycloalkyl (C_{0-3}) alkyl, hetero (C_{5-12}) cycloalkyl (C_{0-3}) alkyl,
 (C_{6-12}) aryl (C_{0-3}) alkyl, hetero (C_{5-12}) aryl (C_{0-3}) alkyl, (C_{9-12}) bicycloaryl (C_{0-3}) alkyl or
 hetero (C_{8-12}) bicycloaryl (C_{0-3}) alkyl or (iii) (C_{3-6}) cycloalkyl (C_{0-3}) alkyl,

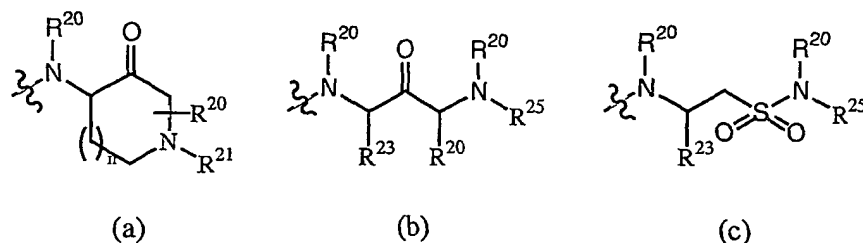
hetero(C₅₋₆)cycloalkyl(C₀₋₃)alkyl, phenyl(C₀₋₃)alkyl or hetero(C₅₋₆)aryl(C₀₋₃)alkyl substituted by -X⁶OR¹⁵, -X⁶SR¹⁵, -X⁶S(O)R¹⁵, -X⁶S(O)₂R¹⁵, -X⁶C(O)R¹⁵, -X⁶C(O)OR¹⁵, -X⁶C(O)NR¹⁵R¹⁶, -X⁶NR¹⁵R¹⁶, -X⁶NR¹⁶C(O)R¹⁵, -X⁶NR¹⁶C(O)OR¹⁵, -X⁶NR¹⁶C(O)NR¹⁵R¹⁶, -X⁶NR¹⁶C(O)OR¹⁶, -X⁶NR¹⁶C(NR¹⁶)NR¹⁵R¹⁶, wherein X⁶ is a

5 bond or methylene, R¹⁵ is (C₃₋₆)cycloalkyl(C₀₋₃)alkyl, hetero(C₅₋₆)cycloalkyl(C₀₋₃)alkyl, phenyl(C₀₋₃)alkyl or hetero(C₅₋₆)aryl(C₀₋₃)alkyl and R¹⁶ is hydrogen or (C₁₋₆)alkyl; wherein R⁴ optionally further contains 1 to 5 substituents which when occurring within an alicyclic or aromatic ring system are radicals independently selected from a group consisting of (C₁₋₆)alkyl, (C₁₋₆)alkylidene, cyano, halo, nitro, halo-substituted (C₁₋₃)alkyl, -X⁶NR¹⁷R¹⁷,

10 -X⁶NR¹⁷C(O)OR¹⁷, -X⁶NR¹⁷C(O)NR¹⁷R¹⁷, -X⁶NR¹⁷C(NR¹⁷)NR¹⁷R¹⁷, -X⁶OR¹⁷, -X⁶SR¹⁷, -X⁶C(O)OR¹⁷, -X⁶C(O)NR¹⁷R¹⁷, -X⁶S(O)₂NR¹⁷R¹⁷, -X⁶P(O)(OR¹⁸)OR¹⁷, -X⁶OP(O)(OR¹⁸)OR¹⁷, -X⁶NR¹⁷C(O)R¹⁸, -X⁶S(O)R¹⁸, -X⁶S(O)₂R¹⁸ and -X⁶C(O)R¹⁸ and when occurring within an aliphatic moiety are radicals independently selected from a group consisting of cyano, halo, nitro, -NR¹⁷R¹⁷, -NR¹⁷C(O)OR¹⁷, -NR¹⁷C(O)NR¹⁷R¹⁷,

15 -NR¹⁷C(NR¹⁷)NR¹⁷R¹⁷, -OR¹⁷, -SR¹⁷, -C(O)OR¹⁷, -C(O)NR¹⁷R¹⁷, -S(O)₂NR¹⁷R¹⁷, -P(O)(OR¹⁷)OR¹⁷, -OP(O)(OR¹⁷)OR¹⁷, -NR¹⁷C(O)R¹⁸, -S(O)R¹⁸, -S(O)₂R¹⁸ and -C(O)R¹⁸, wherein X⁶ is a bond or (C₁₋₆)alkylene, R¹⁷ at each occurrence independently is hydrogen, (C₁₋₆)alkyl or halo-substituted (C₁₋₃)alkyl and R¹⁸ is (C₁₋₆)alkyl or halo-substituted (C₁₋₃)alkyl;

20 X³ is a group of Formula (a), (b) or (c):



n is 0, 1 or 2;

R^{20} is selected from the group consisting of hydrogen, (C_{1-6}) alkyl, (C_{3-12}) cycloalkyl (C_{0-6}) alkyl, hetero (C_{5-12}) cycloalkyl (C_{0-6}) alkyl, (C_{6-12}) aryl (C_{0-6}) alkyl and hetero (C_{5-12}) aryl (C_{0-6}) alkyl;

R^{21} is selected from the group consisting of hydrogen, (C_{1-9}) alkyl, (C_{3-12}) cycloalkyl (C_{0-6}) alkyl, hetero (C_{5-12}) cycloalkyl (C_{0-6}) alkyl, (C_{6-12}) aryl (C_{0-6}) alkyl, hetero (C_{5-12}) aryl (C_{0-6}) alkyl, (C_{9-12}) bicycloaryl (C_{0-3}) alkyl, hetero (C_{8-12}) -bicycloaryl (C_{0-3}) alkyl, $-C(O)R^{26}$, $-C(S)R^{26}$, $-S(O)_2R^{26}$, $-C(O)OR^{26}$, $-C(O)N(R^{26})R^{27}$, $-C(S)N(R^{26})R^{27}$ and $-S(O)_2N(R^{27})R^{26}$;

R^{23} is selected from (C_{1-6}) alkyl, (C_{4-6}) alkenyl, (C_{3-12}) cycloalkyl (C_{0-6}) alkyl, hetero (C_{5-12}) cycloalkyl (C_{0-6}) alkyl, (C_{6-12}) aryl (C_{0-6}) alkyl or hetero (C_{5-12}) aryl (C_{0-6}) alkyl optionally substituted with amino, $-NHC(O)R^{15}$ or $-R^{15}$ wherein R^{15} is as described above;

R^{25} is selected from hydrogen, (C_{1-6}) alkyl, (C_{3-12}) cycloalkyl (C_{0-6}) alkyl, hetero (C_{5-12}) cycloalkyl (C_{0-6}) alkyl, (C_{6-12}) aryl (C_{0-6}) alkyl, hetero (C_{5-13}) aryl (C_{0-6}) alkyl, $-X^4NHR^{15}$, $-X^4S(O)_2R^{26}$ or $-X^4C(O)R^{17}NR^{17}C(O)R^{17}$ wherein R^{15} , R^{17} and X^4 are as described above;

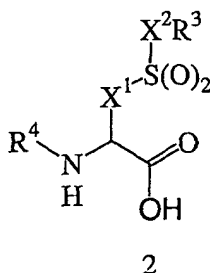
R^{26} is selected from the group consisting of hydrogen, (C_{1-6}) alkyl, (C_{3-12}) cycloalkyl (C_{0-6}) alkyl, hetero (C_{5-12}) cycloalkyl (C_{0-6}) alkyl, (C_{6-12}) aryl (C_{0-6}) alkyl, hetero (C_{5-12}) aryl (C_{0-6}) alkyl, (C_{9-12}) bicycloaryl (C_{0-3}) alkyl and hetero (C_{8-12}) -

bicycloaryl(C₀₋₃)alkyl;

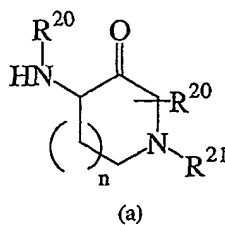
R²⁷ is hydrogen, (C₁₋₆)alkyl, (C₃₋₁₂)cycloalkyl(C₀₋₆)alkyl, hetero(C₅₋₁₂)cycloalkyl(C₀₋₆)alkyl, (C₆₋₁₂)aryl(C₀₋₆)alkyl or hetero(C₅₋₁₂)aryl(C₀₋₆)alkyl;

wherein X³ optionally further contains 1 to 5 substituents which when occurring
 5 within an alicyclic or aromatic ring system are radicals independently selected from a group consisting of (C₁₋₆)alkyl, (C₁₋₆)alkylidene, cyano, halo, nitro, halo-substituted (C₁₋₃)alkyl, -X⁶NR¹⁷R¹⁷, -X⁶NR¹⁷C(O)OR¹⁷, -X⁶NR¹⁷C(O)NR¹⁷R¹⁷,
 -X⁶NR¹⁷C(NR¹⁷)NR¹⁷R¹⁷, -X⁶OR¹⁷, -X⁶C(O)R¹⁷, -X⁶OR¹⁵, -X⁶SR¹⁷, -X⁶C(O)OR¹⁷,
 -X⁶C(O)NR¹⁷R¹⁷, -X⁶S(O)₂NR¹⁷R¹⁷, -X⁶P(O)(OR⁸)OR¹⁷, -X⁶OP(O)(OR⁸)OR¹⁷,
 10 -X⁶NR¹⁷C(O)R¹⁸, -X⁶S(O)R¹⁸, -X⁶S(O)₂R¹⁸ and -X⁶C(O)R¹⁸ and when occurring within an aliphatic moiety are radicals independently selected from a group consisting of cyano, halo, nitro, -NR¹⁷R¹⁷, -NR¹⁷C(O)OR¹⁷, -NR¹⁷C(O)NR¹⁷R¹⁷, -NR¹⁷C(NR¹⁷)NR¹⁷R¹⁷,
 -OR¹⁷, -SR¹⁷, -C(O)OR¹⁷, -C(O)NR¹⁷R¹⁷, -S(O)₂NR¹⁷R¹⁷, -P(O)(OR¹⁷)OR¹⁷,
 -OP(O)(OR¹⁷)OR¹⁷, -NR¹⁷C(O)R¹⁸, -S(O)R¹⁸, -S(O)₂R¹⁸ and -C(O)R¹⁸, wherein R¹⁵,
 15 R¹⁷, R¹⁸ and X⁶ are as described above; said process comprising:

(A) reacting a compound of Formula 2:

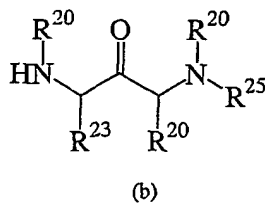


with a compound of the formula (a):



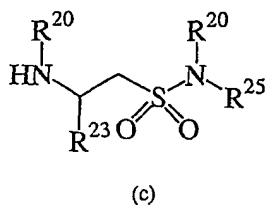
in which X^1 , X^2 , R^3 , R^4 , R^{20} and R^{21} are as defined in the Summary of the Invention for Formula I; or

5 (B) reacting a compound of Formula 2 with a compound of the formula (b):



in which R^{20} , R^{23} and R^{25} are as defined in the Summary of the Invention for Formula I; or

10 (C) reacting a compound of Formula 2 with a compound of the formula (c):

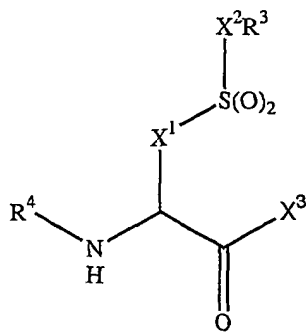


in which R^{20} , R^{23} and R^{25} are as defined in the Summary of the Invention for Formula I; and

15 (D) optionally converting a compound of Formula I into a pharmaceutically acceptable salt;

- (E) optionally converting a salt form of a compound of Formula I to non-salt form;
- (F) optionally converting an unoxidized form of a compound of Formula I into a pharmaceutically acceptable *N*-oxide;
- (G) optionally converting an *N*-oxide form of a compound of Formula I to its unoxidized form;
- (H) optionally resolving an individual isomer of a compound of Formula I from a mixture of isomers;
- (I) optionally converting a non-derivatized compound of Formula I into a pharmaceutically prodrug derivative; and
- (J) optionally converting a prodrug derivative of a compound of Formula I to its non-derivatized form.

13. A compound of Formula Ix:



Ix

in which:

X^1 and X^2 are both methylene or X^1 is ethylene and X^2 is a bond;

R^3 is $-\text{CR}^5=\text{CHR}^6$, $-\text{CR}^5(\text{CR}^6_3)_2$ or $-\text{CR}^7=\text{NR}^8$, wherein R^5 is hydrogen and R^6 is

hydrogen or (C₁₋₄)alkyl or R⁵ and R⁶ together with the atoms to which R⁵ and R⁶ are attached form (C₃₋₁₂)cycloalkenyl, hetero(C₅₋₁₂)cycloalkenyl, (C₆₋₁₂)aryl, hetero(C₆₋₁₂)aryl, (C₉₋₁₂)bicycloaryl or hetero(C₈₋₁₂)bicycloaryl and R⁷ and R⁸ together with the atoms to which R⁷ and R⁸ are attached form hetero(C₅₋₁₂)cycloalkenyl, hetero(C₆₋₁₂)aryl or hetero(C₈₋₁₂)bicycloaryl, wherein R³ optionally is substituted by 1 to 5 radicals independently selected from a group consisting of (C₁₋₄)alkyl, cyano, halo, halo-substituted (C₁₋₄)alkyl, nitro, -X⁴NR⁹R⁹, -X⁴OR⁹, -X⁴SR⁹, -X⁴C(O)NR⁹R⁹, -X⁴C(O)OR⁹, -X⁴S(O)R¹⁰, -X⁴S(O)₂R¹⁰ and -X⁴C(O)R¹⁰, wherein X⁴ is a bond or (C₁₋₂)alkylene, R⁹ at each occurrence independently is hydrogen, (C₁₋₃)alkyl or halo-substituted (C₁₋₃)alkyl and R¹⁰ is (C₁₋₃)alkyl or halo-substituted (C₁₋₃)alkyl; and

R⁴ is -C(O)X⁵R¹¹ or -S(O)₂X⁵R¹¹, wherein X⁵ is a bond, -O- or -NR¹²-, wherein R¹² is hydrogen or (C₁₋₆)alkyl, and R¹¹ is (i) (C₁₋₆)alkyl optionally substituted by -OR¹³, -SR¹³, -S(O)R¹³, -S(O)₂R¹³, -C(O)R¹³, -C(O)OR¹³, -C(O)NR¹³R¹⁴, -NR¹³R¹⁴, -NR¹⁴C(O)R¹³, -NR¹⁴C(O)OR¹³, -NR¹⁴C(O)NR¹³R¹⁴ or -NR¹⁴C(NR¹⁴)NR¹³R¹⁴, wherein R¹³ is (C₃₋₁₂)cycloalkyl(C₀₋₃)alkyl, hetero(C₅₋₁₂)cycloalkyl(C₀₋₃)alkyl, (C₆₋₁₂)aryl(C₀₋₃)alkyl, hetero(C₅₋₁₂)aryl(C₀₋₃)alkyl, (C₉₋₁₂)bicycloaryl(C₀₋₃)alkyl or hetero(C₈₋₁₂)bicycloaryl(C₀₋₃)alkyl and R¹⁴ at each occurrence independently is hydrogen or (C₁₋₆)alkyl, or (ii) (C₃₋₁₂)cycloalkyl(C₀₋₃)alkyl, hetero(C₅₋₁₂)cycloalkyl(C₀₋₃)alkyl, (C₆₋₁₂)aryl(C₀₋₃)alkyl, hetero(C₅₋₁₂)aryl(C₀₋₃)alkyl, (C₉₋₁₂)bicycloaryl(C₀₋₃)alkyl or hetero(C₈₋₁₂)bicycloaryl(C₀₋₃)alkyl or (iii) (C₃₋₆)cycloalkyl(C₀₋₃)alkyl, hetero(C₅₋₆)cycloalkyl(C₀₋₃)alkyl, phenyl(C₀₋₃)alkyl or hetero(C₅₋₆)aryl(C₀₋₃)alkyl substituted by -X⁶OR¹⁵, -X⁶SR¹⁵, -X⁶S(O)R¹⁵, -X⁶S(O)₂R¹⁵, -X⁶C(O)R¹⁵, -X⁶C(O)OR¹⁵, -X⁶C(O)NR¹⁵R¹⁶, -X⁶NR¹⁵R¹⁶, -X⁶NR¹⁶C(O)R¹⁵, -X⁶NR¹⁶C(O)OR¹⁵, -X⁶NR¹⁶C(O)NR¹⁵R¹⁶, -X⁶NR¹⁶C(O)OR¹⁶, -X⁶NR¹⁶C(NR¹⁶)NR¹⁵R¹⁶, wherein X⁶ is a

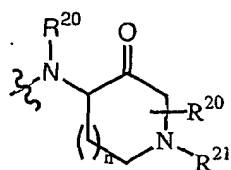
bond or methylene, R^{15} is (C_{3-6}) cycloalkyl (C_{0-3}) alkyl, hetero (C_{5-6}) cycloalkyl (C_{0-3}) alkyl, phenyl (C_{0-3}) alkyl or hetero (C_{5-6}) aryl (C_{0-3}) alkyl and R^{16} is hydrogen or (C_{1-6}) alkyl; wherein R^4 optionally further contains 1 to 5 substituents which when occurring within an alicyclic or aromatic ring system are radicals independently selected from a group consisting of

5 (C_{1-6}) alkyl, (C_{1-6}) alkylidene, cyano, halo, nitro, halo-substituted (C_{1-3}) alkyl, $-X^6NR^{17}R^{17}$, $-X^6NR^{17}C(O)OR^{17}$, $-X^6NR^{17}C(O)NR^{17}R^{17}$, $-X^6NR^{17}C(NR^{17})NR^{17}R^{17}$, $-X^6OR^{17}$, $-X^6SR^{17}$, $-X^6C(O)OR^{17}$, $-X^6C(O)NR^{17}R^{17}$, $-X^6S(O)_2NR^{17}R^{17}$, $-X^6P(O)(OR^{18})OR^{17}$, $-X^6OP(O)(OR^{18})OR^{17}$, $-X^6NR^{17}C(O)R^{18}$, $-X^6S(O)R^{18}$, $-X^6S(O)_2R^{18}$ and $-X^6C(O)R^{18}$ and when occurring within an aliphatic moiety are radicals independently selected from a group

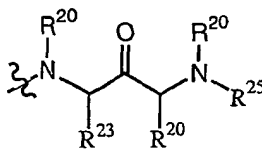
10 consisting of cyano, halo, nitro, $-NR^{17}R^{17}$, $-NR^{17}C(O)OR^{17}$, $-NR^{17}C(O)NR^{17}R^{17}$, $-NR^{17}C(NR^{17})NR^{17}R^{17}$, $-OR^{17}$, $-SR^{17}$, $-C(O)OR^{17}$, $-C(O)NR^{17}R^{17}$, $-S(O)_2NR^{17}R^{17}$, $-P(O)(OR^{17})OR^{17}$, $-OP(O)(OR^{17})OR^{17}$, $-NR^{17}C(O)R^{18}$, $-S(O)R^{18}$, $-S(O)_2R^{18}$ and $-C(O)R^{18}$, wherein X^6 is a bond or (C_{1-6}) alkylene, R^{17} at each occurrence independently is hydrogen, (C_{1-6}) alkyl or halo-substituted (C_{1-3}) alkyl and R^{18} is (C_{1-6}) alkyl or halo-substituted

15 (C_{1-3}) alkyl;

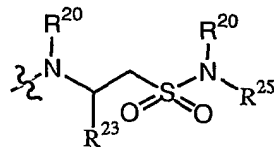
X^3 is a group of Formula (a), (b), (c), (d), (e), (f), (g) or (h):



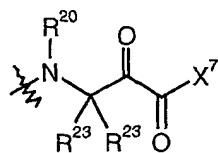
(a)



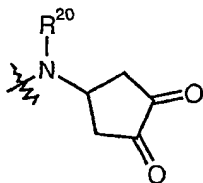
(b)



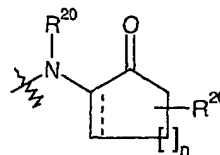
(c)



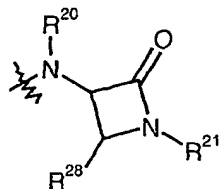
(d)



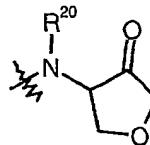
(e)



(f)



(g)



(h)

--- represents a single bond, or a double bond;

X^7 represents aryl, heteroaryl or $NR^{20}R^{25}$;

5 n is 0, 1 or 2;

R^{20} is selected from the group consisting of hydrogen, (C_{1-6}) alkyl, (C_{3-12}) cycloalkyl (C_{0-6}) alkyl, hetero (C_{5-12}) cycloalkyl (C_{0-6}) alkyl, (C_{6-12}) aryl (C_{0-6}) alkyl and hetero (C_{5-12}) aryl (C_{0-6}) alkyl;

10 R^{21} is selected from the group consisting of hydrogen, (C_{1-9}) alkyl, (C_{3-12}) cycloalkyl (C_{0-6}) alkyl, hetero (C_{5-12}) cycloalkyl (C_{0-6}) alkyl, (C_{6-12}) aryl (C_{0-6}) alkyl, hetero (C_{5-12}) aryl (C_{0-6}) alkyl, (C_{9-12}) bicycloaryl (C_{0-3}) alkyl, hetero (C_{8-12}) -bicycloaryl (C_{0-3}) alkyl, $-C(O)R^{26}$, $-C(S)R^{26}$, $-S(O)_2R^{26}$, $-C(O)OR^{26}$, $-C(O)N(R^{26})R^{27}$, $-C(S)N(R^{26})R^{27}$ and $-S(O)_2N(R^{27})R^{26}$;

15 R^{23} is selected from $-H$, (C_{1-6}) alkyl, (C_{4-6}) alkenyl, (C_{3-12}) cycloalkyl (C_{0-6}) alkyl, hetero (C_{5-12}) cycloalkyl (C_{0-6}) alkyl, (C_{6-12}) aryl (C_{0-6}) alkyl or hetero (C_{5-12}) aryl (C_{0-6}) alkyl optionally substituted with amino, $-NHC(O)R^{15}$ or $-R^{15}$ wherein R^{15} is as described above;

R^{25} is selected from hydrogen, (C_{1-6}) alkyl, (C_{3-12}) cycloalkyl (C_{0-6}) alkyl,

hetero(C₅₋₁₂)cycloalkyl(C₀₋₆)alkyl, (C₆₋₁₂)aryl(C₀₋₆)alkyl, hetero(C₅₋₁₃)aryl(C₀₋₆)alkyl, -X⁴NHR¹⁵, -X⁴S(O)₂R²⁶ or -X⁴C(O)R¹⁷NR¹⁷C(O)R¹⁷ wherein R¹⁵, R¹⁷ and X⁴ are as described above;

R²⁶ is selected from the group consisting of hydrogen, (C₁₋₆)alkyl, (C₃₋₁₂)cycloalkyl(C₀₋₆)alkyl, hetero(C₅₋₁₂)cycloalkyl(C₀₋₆)alkyl, (C₆₋₁₂)aryl(C₀₋₆)alkyl, hetero(C₅₋₁₂)aryl(C₀₋₆)alkyl, (C₉₋₁₂)bicycloaryl(C₀₋₃)alkyl and hetero(C₈₋₁₂)-bicycloaryl(C₀₋₃)alkyl;

R²⁷ is hydrogen, (C₁₋₆)alkyl, (C₃₋₁₂)cycloalkyl(C₀₋₆)alkyl, hetero(C₅₋₁₂)cycloalkyl(C₀₋₆)alkyl, (C₆₋₁₂)aryl(C₀₋₆)alkyl or hetero(C₅₋₁₂)aryl(C₀₋₆)alkyl;

R²⁸ is R²⁰ or -O-C(=O)-R²⁹;

R²⁹ is (C₁₋₆)alkyl, (C₃₋₁₂)cycloalkyl(C₀₋₃)alkyl, hetero(C₅₋₁₂)cycloalkyl(C₀₋₃)alkyl, (C₆₋₁₂)aryl(C₀₋₃)alkyl, hetero(C₅₋₁₂)aryl(C₀₋₃)alkyl, (C₉₋₁₂)bicycloaryl(C₀₋₃)alkyl or hetero(C₈₋₁₂)bicycloaryl(C₀₋₃)alkyl;

wherein X³ optionally further contains 1 to 5 substituents which when occurring within an alicyclic or aromatic ring system are radicals independently selected from a group consisting of (C₁₋₆)alkyl, (C₁₋₆)alkylidene, cyano, halo, nitro, halo-substituted (C₁₋₃)alkyl, -X⁶NR¹⁷R¹⁷, -X⁶NR¹⁷C(O)OR¹⁷, -X⁶NR¹⁷C(O)NR¹⁷R¹⁷, -X⁶NR¹⁷C(NR¹⁷)NR¹⁷R¹⁷, -X⁶OR¹⁷, -X⁶C(O)R¹⁷, -X⁶OR¹⁵, -X⁶SR¹⁷, -X⁶C(O)OR¹⁷, -X⁶C(O)NR¹⁷R¹⁷, -X⁶S(O)₂NR¹⁷R¹⁷, -X⁶P(O)(OR⁸)OR¹⁷, -X⁶OP(O)(OR⁸)OR¹⁷, -X⁶NR¹⁷C(O)R¹⁸, -X⁶S(O)R¹⁸, -X⁶S(O)₂R¹⁸ and -X⁶C(O)R¹⁸ and when occurring within an aliphatic moiety are radicals independently selected from a group consisting of cyano, halo, nitro, -NR¹⁷R¹⁷, -NR¹⁷C(O)OR¹⁷, -NR¹⁷C(O)NR¹⁷R¹⁷, -NR¹⁷C(NR¹⁷)NR¹⁷R¹⁷, -OR¹⁷, -SR¹⁷, -C(O)OR¹⁷, -C(O)NR¹⁷R¹⁷, -S(O)₂NR¹⁷R¹⁷, -P(O)(OR¹⁷)OR¹⁷, -OP(O)(OR¹⁷)OR¹⁷, -NR¹⁷C(O)R¹⁸, -S(O)R¹⁸, -S(O)₂R¹⁸ and -C(O)R¹⁸, wherein R¹⁵, R¹⁷, R¹⁸ and X⁶ are as

described above; or

- one of *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers of compounds of formula Ix; or one of pharmaceutically acceptable salts and solvates of such compounds and the *N*-oxide derivatives, prodrug
- 5 derivatives, protected derivatives, individual isomers and mixtures of isomers formula Ix.

14. A compound of claim 13, wherein R²³ is selected from (C₁₋₆)alkyl, (C₄₋₆)alkenyl, (C₃₋₁₂)cycloalkyl(C₀₋₆)alkyl, hetero(C₅₋₁₂)cycloalkyl(C₀₋₆)alkyl, (C₆₋₁₂)aryl(C₀₋₆)alkyl or hetero(C₅₋₁₂)aryl(C₀₋₆)alkyl optionally substituted with amino, -NHC(O)R¹⁵ or -R¹⁵
- 10 wherein R¹⁵ is as described above;

15. A compound of claim 13, selected from the group consisting of:

- Morpholine-4-carboxylic acid [1-(1-benzoyl-4-oxo-pyrrolidin-3-ylcarbamoyl)-2-phenylmethanesulfonyl-ethyl]-amide;
- 15 Morpholine-4-carboxylic acid [1-(1-benzenesulfonyl-4-oxo-pyrrolidin-3-ylcarbamoyl)-2-phenylmethanesulfonyl-ethyl]-amide;
- 4-{2-[(Morpholine-4-carbonyl)-amino]-3-phenylmethanesulfonyl-propionylamino}-3-oxo-azepane-1-carboxylic acid benzyl ester;
- 20 Morpholine-4-carboxylic acid [1-(3-benzenesulfonylamino-2-oxo-propylcarbamoyl)-2-phenylmethanesulfonyl-ethyl]-amide; or
- 25 *N*-{1*S*-[1*S*-(4-Methoxyphenylsulfamoylmethyl)-3-phenylpropylcarbamoyl] 2-benzylsulfonyl-ethyl}-morpholine-4-carboxamide.

16. A compound of claim 13, selected from the group consisting of:

- 30 Morpholine-4-carboxylic acid [(*R*)-1-(6-oxo-cyclohex-1-enylcarbamoyl)-2-phenylmethanesulfonyl-ethyl]-amide;
- Morpholine-4-carboxylic acid [(*R*)-2-cyclopropylmethanesulfonyl-1-(6-oxo-cyclohex-1-enylcarbamoyl)-ethyl]-amide;

Morpholine-4-carboxylic acid [(R)-1-(3,4-dioxo-cyclopentylcarbamoyl)-2-phenylmethanesulfonyl-ethyl]-amide;

- 5 Morpholine-4-carboxylic acid [2-(2-difluoromethoxy-phenylmethanesulfonyl)-1-(2-oxo-cyclohexylcarbamoyl)-ethyl]-amide;

Morpholine-4-carboxylic acid [2-(2-difluoromethoxy-phenylmethanesulfonyl)-1-(2-oxo-cyclopentylcarbamoyl)-ethyl]-amide;

10

Morpholine-4-carboxylic acid [2-(2-difluoromethoxy-phenylmethanesulfonyl)-1-(2-oxo-cyclobutylcarbamoyl)-ethyl]-amide;

15

(Morpholine-4-carboxylic acid [1-(2-benzylcarbamoyl-2-oxo-ethylcarbamoyl)-2-phenylmethanesulfonyl-ethyl]-amide);

Acetic acid 3-{2-[(morpholine-4-carbonyl)-amino]-3-phenylmethanesulfonyl-propionylamino}-4-oxo-azetidin-2-yl ester;

20

Morpholine-4-carboxylic acid [1-(2-hydroxy-1,1-dimethyl-3-oxo-3-phenyl-propylcarbamoyl)-2-phenylmethanesulfonyl-ethyl]-amide;

Morpholine-4-carboxylic acid [1-(4-oxo-tetrahydro-furan-3-ylcarbamoyl)-2-phenylmethanesulfonyl-ethyl]-amide; or

25

Morpholine-4-carboxylic acid [2-(2-difluoromethoxy-phenylmethanesulfonyl)-1-(1,1-dimethyl-2,3-dioxo-3-phenyl-propylcarbamoyl)-ethyl]-amide.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 02/29323

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07C317/48 C07C317/50 C07D207/24 C07D223/08 C07D295/20
 C07D307/32 C07K5/065 A61K31/10 A61P19/02 A61P29/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07C C07D C07K A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

BEILSTEIN Data, WPI Data, EPO-Internal, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 01 19796 A (AXYS PHARMARCEUTICALS) 22 March 2001 (2001-03-22) cited in the application page 2 -page 4; claims 1,11-13; examples ---	1-16
A	WO 96 30353 A (ARRIS PHARMACEUTICAL) 3 October 1996 (1996-10-03) page 3 -page 4; table 2 ---	1-16
A	WO 00 69855 A (MEDIVIR UK) 23 November 2000 (2000-11-23) page 2 -page 3 ---	13-16
A	WO 00 59881 A (NAEJA PHARMACEUTICAL) 12 October 2000 (2000-10-12) page 3 -page 4 -----	13-16

☐ Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

* Special categories of cited documents:

A document defining the general state of the art which is not considered to be of particular relevance

E earlier document but published on or after the international filing date

L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

O document referring to an oral disclosure, use, exhibition or other means

P document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

& document member of the same patent family

Date of the actual completion of the international search

5 December 2002

Date of mailing of the international search report

19/12/2002

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FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-8,12-14

The scope of the claims 1-8,12-14, in as far as the expressions "prodrug derivatives" and "protected derivatives" are concerned, is so unclear (Article 6 PCT) that a meaningful International Search is impossible with regard to these expressions.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 02/29323

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 10 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☒ Claims Nos.: 1-8, 12-14
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 02/29323

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 0119796	A	22-03-2001	AU 7490900 A	17-04-2001
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			TW 470750 B	01-01-2002
			WO 9630353 A1	03-10-1996
			US 5776718 A	07-07-1998
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			BR 0010553 A	02-07-2002
			EP 1178986 A2	13-02-2002
			WO 0069855 A2	23-11-2000
WO 0059881	A	12-10-2000	AU 3570000 A	23-10-2000
			EP 1165506 A1	02-01-2002
			WO 0059881 A1	12-10-2000